antioxidants

MDPI

Review

Multifactorial Flight Fatigue and Its Intervention Strategies

Ruilong Zheng [1,†], Yuyue Yang [1,†], Feng Li [2], Yu Kong [1], Jiangang Long [1,*] and Xuyun Liu [1,*]

[1] Institute of Mitochondrial Biology and Medicine, Xi'an Key Laboratory of Aging Biology, The Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, China; yukong@xjtu.edu.cn (Y.K.)
[2] Research Department, Air Force Medical Center, Air Force Medical University, Beijing 100142, China
* Correspondence: jglong@xjtu.edu.cn (J.L.); xuyunliu@xjtu.edu.cn (X.L.)
† These authors contributed equally to this work.

Abstract

Flight fatigue is a major operational concern in both civil and military aviation, arising from multiple stressors, including sustained cognitive workload, circadian disruption, hypoxia, and high-G exposure. Despite growing research interest, the relationships among operational stressors, fatigue-related phenotypes, and their potential biological underpinnings remain fragmented. This review synthesizes the major stress scenarios encountered in aviation, organizes their functional consequences into three phenotypic domains, and examines the biological pathways potentially associated with these alterations, with particular attention to oxidative stress and mitochondrial dysfunction. Based on this evidence, we propose a scenario–phenotype–pathway/target (SPT) framework as a conceptual, evidence-informed approach to organizing potential relationships among flight-related stressors, fatigue phenotypes, and relevant biological pathways and molecular targets. We further review pharmacological, nutritional, behavioral, and environmental interventions, highlighting the emerging application of network pharmacology as a hypothesis-generating approach for identifying multi-target natural product-based strategies potentially relevant to fatigue regulation and oxidative stress. By integrating operational stressors, phenotypic manifestations, potential biological mechanisms, and intervention approaches, this review provides a structured basis for understanding flight fatigue, identifying research gaps, and guiding the development and future validation of potential anti-fatigue strategies targeting oxidative stress and related biological pathways.

Keywords: flight fatigue; oxidative stress; mitochondrial dysfunction; neuroinflammation; natural products; antioxidants; network pharmacology

Academic Editor: Giancarlo Aldini

Received: 17 September 2026
Revised: 15 November 2026
Accepted: 19 November 2026
Published: 23 November 2026

Copyright: © 2026 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.

1. Introduction

Flight fatigue is a generally reversible physiological state characterized by impairments in physiological, neurocognitive, and psychological functions that arise during aviation operations as a result of sustained workload, insufficient sleep, circadian disruption, and environmental stressors [1,2].

As one of the major risk factors in aviation safety, flight fatigue has been associated with approximately 21–23% of major aviation accidents [2]. However, its underlying biological basis remains insufficiently understood. Modern military aviation missions are frequently accompanied by multiple operational stressors, including prolonged flight

duration, high-maneuvering flight, cognitively demanding decision-making tasks, and exposure to complex operational environments [3]. These stressors include environmental factors such as temperature fluctuations [4], noise and vibration [5], chronic hypobaric hypoxia [6], and high acceleration exposure [7,8], as well as mission-related factors including sleep deprivation [9], circadian rhythm disruption [10], and sustained cognitive workload [11]. The combined effects of these operational and environmental stressors substantially increase fatigue risk in military aviation. Under such conditions, fatigue not only increases the risk of aviation accidents and human error but also impairs situational awareness, cognitive flexibility, and task performance, thereby compromising mission effectiveness and military readiness [3]. Consequently, flight fatigue has become an important area of concern in aviation medicine and occupational health research.

Flight fatigue is a multifactorial condition resulting from the interaction of environmental stressors, sleep-related stressors, and task-related stressors, giving rise to diverse physical, neurocognitive, and psychological phenotypes. Understanding how these operational exposures are linked to their underlying biological mechanisms is therefore essential for improving fatigue assessment and intervention.

This review summarizes current evidence on flight fatigue by integrating operational stress scenarios, fatigue-related phenotypes, biological pathways, and molecular targets. We further organize these findings within a Scenario–Phenotype–Pathway/Target (SPT) framework to provide a structured perspective on the biological basis of flight fatigue. Furthermore, pharmaceutical and nutritional interventions, together with behavioral and environmental interventions, are reviewed. Given the multifactorial nature of flight fatigue and the involvement of multiple interacting pathways and molecular targets, multi-component natural products have emerged as promising candidates for multi-target anti-fatigue intervention. In this context, network pharmacology is discussed as a systems-level framework for identifying promising natural products and herbal formulations, elucidating their multi-target molecular mechanisms, and guiding the rational design and optimization of anti-fatigue formulations.

2. Stressors and Physiological Responses

The development of flight fatigue is highly dependent on the specific stress scenarios encountered during flight operations [7–12]. Different flight environments and mission conditions may exert selective effects on physiological and neurobiological processes, thereby producing distinct patterns of functional impairment and fatigue manifestations [13]. Therefore, categorizing flight-related stress scenarios based on actual operational exposures is essential for understanding the underlying causes of flight fatigue and its potential regulatory mechanisms. Based on current evidence from aviation medicine and neuroscience, flight fatigue-related stressors can be broadly classified into three categories: environmental stressors, sleep-related stressors, and task load-related stressors.

2.1. Environmental Stressors

2.1.1. High Acceleration (+Gz) Exposure

In modern aviation operations, pilots are exposed to varying levels of positive acceleration (+Gz) during flight. Such stress is primarily encountered during takeoff, climb, turning maneuvers, evasive actions, and tactical operations. In military transport aviation, maneuver-induced acceleration exposure can reach approximately +3.5 Gz during operational flight profiles [14], whereas acceleration may reach up to +9Gz during high-performance fighter maneuvers [15]. Studies have shown that increasing +Gz exposure induces a series of characteristic visual and consciousness-related disturbances. Loss of peripheral vision typically occurs at approximately 3.4–4.8 G, blackout is

commonly observed at approximately 4.0–5.6 G, and loss of consciousness may occur within the range of approximately 4.5–6.3 G [16]. These manifestations are acute responses to high-G stress rather than direct indicators of fatigue. However, repeated or prolonged exposure may potentially contribute to fatigue development and reduced operational performance [17].

At the physiological level, high-G exposure primarily induces blood pooling in the lower extremities, leading to reduced cerebral perfusion pressure [18]. This response subsequently triggers sympathetic nervous system activation and cardiovascular compensatory mechanisms to maintain cerebral blood flow [19]. Repeated or prolonged exposure increases the regulatory burden on the cardiovascular system while simultaneously imposing significant mechanical stress on the neck and trunk musculature, thereby generating multi-system physiological strain [17]. Under conditions of long-term accumulation, these effects may constitute an important environmental basis for the development of flight fatigue.

2.1.2. Noise and Vibration

In both civil and military aviation, pilots are chronically exposed to the combined physical stress of continuous noise and mechanical vibration. Noise levels within modern aircraft cockpits generally exceed 70 dB(A) and may further increase during specific phases of flight. This acoustic environment is generated by the combined effects of engine noise, aerodynamic noise, and structural vibration. Previous studies have shown that physiological responses can be significantly altered when noise levels exceed 70 dB(A) [20]. Meanwhile, pilots may also be exposed to mechanical vibration and airborne noise during flight. A study conducted under specific military aircraft ground-test conditions reported a higher-frequency resonance response in the upper torso at approximately 63–100 Hz [21]. Such combined noise–vibration exposure is typically continuous or intermittent in nature, and its physiological effects may accumulate with increasing flight duration.

From a physiological perspective, persistent noise and vibration primarily exert long-term effects on central regulatory systems by increasing sensory input load rather than directly causing damage to sensory organs [5]. Studies have demonstrated that noise exposure activates the hypothalamic–pituitary–adrenal (HPA) axis and disrupts the homeostasis of monoamine neurotransmitters, including dopamine and norepinephrine [22]. In addition, noise exposure may interfere with processes related to synaptic plasticity, thereby reducing the efficiency of information processing within neural networks [23]. Functionally, these stressors are more likely to impair response stability and fine motor performance [24], suggesting that their primary effects occur at the level of central nervous system regulation rather than peripheral arousal systems.

2.1.3. Chronic Hypobaric Hypoxia

Chronic hypobaric hypoxia is a relatively subtle yet persistent environmental stressor in aviation settings [25,26]. During flight operations, the degree of hypoxic exposure is primarily determined by cabin-equivalent altitude and cabin pressurization conditions. In typical commercial aviation environments, cabin-equivalent altitude is generally maintained at approximately 2400–2500 m, corresponding to a mild but sustained hypoxic load [27]. In military high-altitude operations or decompression environments, however, equivalent exposure altitude may reach 3000 m or higher, substantially increasing hypoxic stress [28]. Studies have demonstrated that within the moderate hypoxia range of 2500–4000 m, significant declines in cognitive performance, reaction time, and visual function may occur even in the absence of obvious subjective symptoms, indicating the insidious nature of hypoxia-induced functional impairment [29].

At the physiological level, chronic hypobaric hypoxia reduces arterial oxygen availability, leading to decreased cerebral oxygen delivery and impaired aerobic energy production. Mechanistic studies indicate that these changes may compromise cerebral metabolic homeostasis and reduce the capacity to sustain normal neuronal activity [30,31]. As a result, pilots may exhibit reduced vigilance, impaired executive function, slower decision-making, and diminished operational performance, especially during prolonged or high-altitude missions [32].

2.1.4. Temperature Stress

Flight personnel are frequently exposed to varying degrees of temperature stress within enclosed cockpit environments, including heat stress, cold stress, and rapid temperature fluctuations. Studies have shown that exposure to high-temperature environments significantly increases core body temperature, promotes muscular fatigue, and elevates the likelihood of operational errors. For example, under an ambient temperature of 38 °C, core body temperature may reach 38.0 °C within 55 min, while target engagement error rates increase by approximately 50% compared with those observed under thermally comfortable conditions [33]. Previous studies have reported that cockpit temperatures may rise to 40 °C or higher during certain tactical and transport missions. Under prolonged flight or standby conditions, exposure durations may extend from several tens of minutes to several hours [34]. Unlike short-duration stressors such as high-G exposure, thermal stress is generally characterized by moderate intensity and prolonged duration, making it an important environmental factor influencing operational tolerance in aviators.

At the physiological level, thermal stress increases thermoregulatory burden and metabolic demand [33], enhances sympathetic nervous system activity, and alters circulatory regulation. It may also accelerate fluid loss and energy expenditure. Functionally, both heat and cold exposure can impair sustained attention and operational stability, leading to prolonged reaction times and increased error rates [35,36].

2.2. Sleep-Related Stressors

2.2.1. Sleep Deprivation

In military aviation, aircrew commonly experience insufficient sleep owing to operational demands such as night missions, extended flight duty periods, rapid deployment across time zones, and prolonged readiness requirements. Studies have shown that under actual flight-duty conditions, pilots typically obtain less sleep than recommended, with an average sleep duration of approximately 6 h during consecutive work periods [37], which is substantially below the recommended 7–9 h of sleep for healthy adults. Operational demands such as night flights and transmeridian missions may repeatedly disrupt sleep recovery across multiple consecutive workdays, causing sleep insufficiency to exhibit both cyclical and cumulative characteristics. As a result, progressive sleep debt accumulates over time, making sleep deprivation one of the most prevalent physiological stressors in aviation operations.

Studies in pilots have shown that sleep deprivation impairs alertness and flight-relevant performance [38]. Mechanistic evidence from experimental and human studies indicates that both acute and chronic sleep loss can suppress prefrontal cortical activity and impair synaptic plasticity [39,40], and that sleep deprivation disrupts wake-promoting neurotransmitter systems, including norepinephrine and acetylcholine, which are essential for maintaining alertness and information-processing capacity [41,42]. Functionally, prolonged partial sleep deprivation not only reduces operational stability but also increases subjective fatigue and decreases task endurance.

2.2.2. Circadian Rhythm Disruption

Circadian rhythm disruption refers to a mismatch between endogenous biological rhythms and external environmental cues [43,44]. In aviation settings, it is primarily associated with operational factors such as transmeridian flights and shift-work schedules. Studies have reported that more than 70% of flight scheduling patterns result in varying degrees of circadian misalignment [10]. Under these conditions, the prevalence of sleep disturbances may reach 71%, while fatigue symptoms are reported by up to 89% of affected personnel [45], indicating that circadian disruption is highly prevalent in aviation operations.

At the physiological level, circadian rhythm disruption primarily affects endogenous biological clock networks, resulting in alterations in sleep architecture and disturbances in hormonal rhythmicity [46]. Functionally, it is characterized by reduced efficiency in attention, memory, and executive function, as well as impaired emotional stability, making it an important contributor to flight fatigue.

2.3. Task Load and Psychological Stress

Task load and psychological stress are common stressors in aviation operations and encompass multiple components, including multitasking, time pressure, situational monitoring, and cognitive workload. Studies using both flight simulators and real-flight settings have demonstrated that pilots experience substantially higher mental workload during critical flight phases, such as turning maneuvers and landing, compared with the cruise phase [47]. Assessments using the NASA Task Load Index (NASA-TLX) have further shown significantly elevated subjective workload scores during these operationally demanding phases, indicating substantial cognitive and psychological demands [48].

From a mechanistic perspective, sustained high workload and task-related psychological stress can chronically activate the HPA axis, thereby altering cortisol secretion patterns and impairing prefrontal cortical function, ultimately disrupting complex cognitive processes [49,50]. Functionally, these effects are primarily manifested as declines in cognitive performance and difficulties in emotional regulation [51].

Although the stressors described above can all contribute to the development of flight fatigue, they differ substantially in their physiological and neuroregulatory characteristics. These differences largely determine the predominant forms of functional impairment and their underlying regulatory pathways [11]. In general, environmental stressors primarily affect physiological homeostasis and energy metabolism, whereas sleep-related disturbances and high workload conditions exert more direct effects on central nervous system regulatory networks, resulting in alterations in cognitive and behavioral performance.

3. Functional Phenotypes and Assessment of Flight Fatigue

Flight fatigue should not be regarded as a single condition but rather as a collection of phenotypes with distinct functional characteristics and biological underpinnings. Different flight-related stressors may induce specific fatigue phenotypes through diverse physiological mechanisms, resulting in characteristic patterns of functional impairment [7–9,16]. The classification of these phenotypes facilitates the translation of complex external stress exposures into identifiable functional outcomes. Considering the operational demands of aviation tasks, flight fatigue-related manifestations can generally be categorized into three domains: reduced physical and physiological tolerance, impaired neurocognitive function, and compromised psychological and emotional regulation. These domains interact with one another and collectively determine overall

operational performance [52]. These domains are intended to facilitate the synthesis of heterogeneous findings rather than to represent mutually exclusive diagnostic categories. They may overlap within the same individual and vary according to the type, intensity, and duration of exposure.

3.1. Reduced Physical and Physiological Tolerance

3.1.1. Reduced Operational Tolerance

Reduced operational tolerance differs from simple peripheral muscular fatigue and is more accurately characterized by a mismatch between central neural drive and peripheral energy supply [53]. It is typically manifested as a progressive decline in operational stability during sustained tasks, resulting in reduced task endurance and the accumulation of performance errors. The underlying mechanisms involve impaired mitochondrial function, reduced energy metabolic efficiency, and autonomic nervous system dysregulation [54,55], which collectively limit the ability of the organism to maintain energy homeostasis and stable neural activation under prolonged workload conditions.

Based on these characteristics, this phenotype is commonly evaluated through sustained task performance and heart rate variability (HRV). Operational error rates reflect functional deterioration at the behavioral output level, whereas HRV indices such as the root mean square of successive differences (RMSSD) provide indicators of autonomic regulatory status. This phenotype is frequently observed under heat stress [56], hypoxic exposure [6], and high-G environments [57]. Under heat stress at 38 °C, operational error rates during flight-related tasks may increase to approximately 64% ($p <$ 0.01) [33]. Under acute hypoxic conditions, arterial oxygen saturation decreases from approximately 97% to 74% ($p < 0.001$), accompanied by an approximately 12% reduction in RMSSD, indicating substantial impairment of autonomic regulation and tolerance to sustained task performance [58]. Overall, this phenotype tends to exhibit cumulative deterioration under prolonged or combined stress conditions.

3.1.2. Impaired Physiological Homeostasis

Impaired physiological homeostasis refers to a reduced capacity to maintain internal physiological stability under stress conditions and is typically manifested as abnormalities in thermoregulation and reduced respiratory control efficiency [59]. This process is primarily associated with dysregulation of autonomic nervous system and neuroendocrine function [60], thereby diminishing the body's ability to maintain circulatory, metabolic, and respiratory stability in response to environmental challenges. Unlike reduced operational tolerance, this phenotype does not necessarily manifest as subjective fatigue but may substantially decrease physiological compensatory capacity during extreme or unexpected situations [61].

Assessment of this phenotype is generally based on thermoregulatory indices, pulmonary function parameters, and heart rate variability measures. For example, short-term exposure to an ambient temperature of 47 °C can increase core body temperature by approximately 0.68–1.37 °C [62]. Under acute hypoxic conditions, forced expiratory volume in one second (FEV_1) decreases by approximately 5.4%, accompanied by a significant reduction in heart rate variability, indicating impaired respiratory and cardiovascular regulatory capacity [58]. This phenotype primarily reflects a decline in fundamental physiological regulatory functions and may amplify functional impairments when multiple stressors are present simultaneously.

3.2. Neurocognitive Impairment

3.2.1. Impaired Vigilance Maintenance

Impaired vigilance maintenance is one of the most sensitive cognitive phenotypes associated with sleep deprivation and circadian rhythm disruption. It is primarily characterized by prolonged reaction times and reduced detection performance during sustained attention tasks [63]. The hallmark of this phenotype is reduced response stability, whereby individuals exhibit intermittent lapses of attention and performance fluctuations despite appearing subjectively awake. These alterations are closely associated with reduced activity within arousal-maintenance systems and diminished function of prefrontal regulatory networks [64], reflecting a disruption in the coordination between central arousal and cognitive control processes.

Based on these characteristics, the Psychomotor Vigilance Task (PVT) has been widely used to quantify this phenotype. By measuring indicators such as reaction time delays and lapses, the PVT provides a sensitive assessment of vigilance performance [65]. In a study of sleep-deprived Air Force pilots, vigilance performance decreased by approximately 70% following 24 h of sleep deprivation, accompanied by significant prolongation of mean reaction time and marked increases in lapse frequency and response variability [66]. Overall, this phenotype exhibits high sensitivity to sleep–circadian disturbances and is characterized by pronounced temporal dependence and performance fluctuations.

3.2.2. Impaired Executive Function and Working Memory

Impaired executive function and working memory are primarily manifested as reduced cognitive flexibility, weakened inhibitory control, and diminished efficiency of information updating, reflecting compromised prefrontal cortical regulation [67]. Unlike impaired vigilance, this phenotype is more commonly characterized by increased errors and unstable performance during complex tasks, indicating deficits in higher-order cognitive processes. It is frequently observed under conditions of chronic hypoxia [68], sustained workload, and prolonged psychological stress [69]. The underlying neural basis primarily involves alterations in functional connectivity between the prefrontal cortex and associated regions, including the parietal cortex and striatum.

Accordingly, executive function and working memory are commonly assessed using multitasking paradigms and working memory tasks. Indicators such as task errors, response delays, and task completion efficiency can reflect changes in prefrontal regulatory capacity. Preclinical studies of high-altitude exposure (animal models and human organoids) suggest that prolonged hypoxia may impair working-memory-related neural function [70]. Separately, flight-simulator experiments have demonstrated that increasing task load can increase target-tracking errors (from 21.67 ± 3.71 mm to 26.07 ± 6.50 mm) and prolong response latency [71]. These findings provide complementary evidence from environmental exposure and aviation-related task performance, although they do not by themselves establish a direct molecular mechanism of flight fatigue.

3.2.3. Altered Decision-Making and Risk Assessment

Altered decision-making and risk assessment are primarily characterized by changes in risk preference, delayed decision-making, and reduced ability to adapt behavioral strategies. This phenotype is commonly observed under conditions of high stress and multitasking workload [72]. Unlike general cognitive slowing, it is mainly reflected in shifts in risk evaluation processes, resulting in altered judgments of risk and reward under uncertain conditions. Behavioral studies have demonstrated that Acute stress can alter risk preference and decision-making behavior under conditions of uncertainty [73].

The underlying mechanisms involve dysregulation of prefrontal control networks and their modulation of limbic structures, including the amygdala and striatum [74].

These neural alterations may disrupt reward processing, value representation, and adaptive decision-making under uncertain conditions [75].

3.3. Compromised Psychological and Emotional Regulation

3.3.1. Fatigue-Related Affective and Motivational Changes

Fatigue-related psychological changes may involve alterations in mood, motivation, subjective well-being, and the ability to sustain engagement during prolonged or demanding tasks. This phenotype is commonly accompanied by increased subjective fatigue, reduced attention, and decreased motivation [76]. It reflects a progressive decline in the ability to maintain psychological stability and task engagement during prolonged workload, ultimately representing an imbalance between psychological regulation and neuroadaptive processes.

Evidence from simulated long-duration flight missions suggests that increasing fatigue severity is associated with a decline in positive affect [77], whereas positive correlations have been observed between fatigue and feelings of boredom or low mood [78]. These findings suggest that affective and motivational changes may accompany fatigue under sustained operational demands.

From an assessment perspective, this phenotype is commonly evaluated using subjective fatigue scales and mood-state questionnaires, together with measures of task performance [79]. Overall, this phenotype reflects a reduced capacity to sustain effective cognitive, emotional, and motivational functioning under prolonged operational demands, making it an important indicator of fatigue-related deterioration in mission performance and psychological readiness.

3.3.2. Emotional Dysregulation

Emotional dysregulation is primarily characterized by increased emotional instability and elevated risks of anxiety and depression, particularly when sleep insufficiency is combined with psychological stress [80]. This phenotype is commonly quantified using psychometric instruments assessing anxiety and depressive symptoms and is often validated through epidemiological risk analyses. For example, a study involving 7055 Chinese civil aviation pilots reported that individuals sleeping less than 7 h per night exhibited approximately 2.491-fold higher risk of depression and 2.555-fold higher risk of anxiety compared with those obtaining adequate sleep [81], suggesting a high sensitivity of emotional regulation to sleep-related disturbances.

Furthermore, these emotional alterations rarely occur in isolation. Rather, they frequently co-occur with cognitive and physiological phenotypes under specific flight-related stress conditions, forming characteristic phenotype combinations [82].

4. Core Biological Pathways and Key Targets

Building on the seven flight-related stress scenarios and three major fatigue-related phenotypic domains established in the preceding sections, we synthesized the relevant literature to identify biological pathways and molecular targets potentially associated with these phenotypes. The synthesis focused on mechanistic evidence linking the identified scenarios and functional alterations to underlying biological processes, with inclusion guided by biological plausibility and relevance to aviation-related stress. This phenotype-oriented approach yielded five overarching pathway categories: mitochondrial metabolism, neuroinflammation, neuroendocrine regulation, arousal and circadian regulation, and neurovascular and cerebral perfusion regulation. Representative pathways and molecular targets were then organized within these

categories according to their reported biological functions and potential relevance to the fatigue-related phenotypes discussed above.

These categories provide an organizing structure for the available mechanistic evidence rather than an exhaustive or mutually exclusive classification of flight-fatigue biology. Processes such as neurotransmitter signaling, synaptic plasticity, autonomic regulation, and fluid and electrolyte homeostasis were not considered biologically irrelevant; rather, they were not designated as separate top-level categories in the present framework. Their relevance may overlap with, or extend across, the five categories, depending on the underlying physiological context.

The evidence supporting these pathways varies in both source and study design. Aviation-personnel studies provide direct operational context, whereas studies conducted under aviation-related simulated conditions examine selected aspects of operational exposure. Research in other human populations, animal models, and in vitro systems provides complementary physiological or mechanistic evidence. Observational associations, controlled experimental findings, and mechanistic or computational predictions support different levels of inference and should not be treated as equivalent. Accordingly, the pathway summaries below distinguish the available evidence base from the potential relevance of each pathway to flight fatigue. The proposed associations are intended to support evidence integration and hypothesis generation rather than to establish uniformly validated causal mechanisms.

4.1. Mitochondrial Metabolism Pathways and Key Targets

Under flight-related stress conditions, an imbalance between energy supply and demand may contribute to the development of fatigue. The regulation of this process involves multiple interconnected biological pathways. As the primary organelle responsible for energy metabolism, mitochondria serve as a central hub in these regulatory processes [83,84]. Within energy-sensing and metabolic regulatory pathways, the AMPK signaling pathway, with AMPK as its core regulator, contributes to the regulation of energy production and consumption through downstream factors such as ACC and PGC-1α, thereby supporting metabolic homeostasis under energy stress [85]. In addition, mTOR- and FoxO-related pathways participate in energy redistribution by regulating protein synthesis and antioxidant processes [86]. However, the effects of AMPK and mTOR pathway modulation depend on tissue type, metabolic state, and the duration and intensity of stress exposure; therefore, AMPK activation and mTOR inhibition should not be regarded as universally beneficial strategies for fatigue management. In pathways related to mitochondrial biogenesis and function, PGC-1α, NRF1, and TFAM are involved in the coordinated regulation of mitochondrial biogenesis and the expression of genes required for mitochondrial function, including oxidative phosphorylation [87]. In mitochondrial quality-control pathways, PINK1/Parkin-mediated mitophagy contributes to the removal of damaged mitochondria [88], whereas MFN1/2 and OPA1 primarily regulate mitochondrial dynamics, particularly mitochondrial fusion [89].

Meanwhile, in oxidative stress and metabolic adaptation pathways, the Nrf2 signaling pathway and glutathione metabolism pathway contribute to the activation of antioxidant responses and the clearance of reactive oxygen species (ROS) [90,91]. Importantly, the relationship between oxidative stress and mitochondrial dysfunction is potentially bidirectional: excessive reactive oxygen species (ROS) can damage mitochondrial components and impair mitochondrial function, while mitochondrial dysfunction can, in turn, increase ROS production and exacerbate redox imbalance [92]. Oxidative stress-related changes have also been reported in military pilots. A study of 35 German Air Force fighter pilots across 145 Eurofighter training flights found an 11.1%

decrease in fractional exhaled nitric oxide (FeNO) and a 15.7% mean increase in urinary 8-hydroxy-2′-deoxyguanosine (8-OHdG) after flight, suggesting airway and systemic oxidative stress associated with +Gz maneuvers and positive-pressure breathing[93]. Similarly, A study of Greek military pilots exposed to simulated hypoxic flight conditions found that redox responses varied with flight experience: experienced pilots showed increased glutathione (GSH) and decreased total antioxidant capacity (TAC), whereas trainees exhibited increased catalase (CAT) activity and TAC. Neither group showed significant changes in thiobarbituric acid-reactive substances (TBARS) or protein carbonyls [94]. Similarly, a study of Taiwanese aircrew undergoing hypobaric chamber training at simulated altitudes of 25,000 or 35,000 ft reported a significant decrease in Trolox equivalent antioxidant capacity (TEAC) after training, indicating reduced antioxidant capacity [95]. These findings indicate that flight-related exposure can alter redox balance, although responses may vary with flight experience, age, and exposure conditions.

Collectively, these interconnected pathways contribute to the regulation of mitochondrial energy metabolism and redox homeostasis and may be relevant to physical and cognitive performance under fatigue-related conditions (Table 1).

Table 1. Key Mitochondrial Pathways and Their Relevance to Flight Fatigue.

Pathway Category	Specific Pathway	Key Targets	Potential Relevance to Fatigue Regulation	Major Associated Scenarios	Major Fatigue Phenotypes	Evidence Base (Source/Design /Aviation Relevance)
Energy sensing and metabolic regulation	AMPK signaling pathway [85]	AMPK, PGC-1α	Potential modulation of energy homeostasis	Hypobaric hypoxia, high workload	Reduced operational tolerance	AN/MECH/IND
	mTOR signaling pathway [96]	mTOR, LARP1	Context-dependent modulation of energy metabolism and protein synthesis	High workload	Impaired executive function and working memory	Review/Review /IND
	Insulin signaling pathway [97]	PI3K, Akt, mTOR	Potential regulation of metabolic homeostasis	circadian disruption	Impaired physiological homeostasis	Review/Review /IND
	FoxO signaling pathway [86]	FoxO, SIRT1, Nrf2, PGC-1α	Potential regulation of antioxidant defense and metabolism	Thermal stress, chronic hypobaric hypoxia	Impaired physiological homeostasis	Review/Review /IND
Mitochondrial energy production	Glycolysis pathway [98]	HK2, PFK, LDHA	Context-dependent regulation of glucose metabolism	High workload, hypoxia	Reduced operational tolerance	Review/Review /IND
	Oxidative phosphorylation pathway [87]	PGC-1α, NRF1, TFAM	Potential support of mitochondrial energy production	High workload, hypoxia	Reduced operational tolerance	AN/MECH/IND
	Fatty acid degradation pathway [99]	CPT1, CACT	Potential regulation of fatty acid oxidation	Psychological stress, high workload	Reduced operational tolerance	Review/Review /IND
Mitochondrial quality control	Mitochondrial autophagy pathway [88]	PINK1, Parkin	Potential regulation of mitochondrial quality control	Sleep deprivation, hypoxia	Impaired physiological homeostasis	Review/Review /IND

	Mitochondrial dynamics and fusion [89]	MIEFs, Mfn1/2, OPA1	Maintenance of mitochondrial dynamics and homeostasis	High workload, hypoxia	Reduced operational tolerance	IV/MECH/IND
	Mitochondrial biogenesis [87]	PGC-1α, NRF1, TFAM	Maintenance of mitochondrial dynamics and homeostasis	High workload, hypoxia	Reduced operational tolerance	AN/MECH/IND
Oxidative stress defense	Nrf2 signaling pathway [91]	Nrf2, HO-1	Potential enhancement of antioxidant responses	Temperature changes, noise, high G exposure	Impaired physiological homeostasis	AN/MECH/IND
	Glutathione metabolic pathway [90]	GSH, GPX, SOD2	Potential support of antioxidant defense	Temperature changes, hypoxia	Impaired physiological homeostasis	AN/MECH/IND

Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; mTOR, mechanistic target of rapamycin; LARP1, La-related protein 1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; FoxO, forkhead box O; SIRT1, sirtuin 1; Nrf2, nuclear factor erythroid 2-related factor 2; HK2, hexokinase 2; PFK, phosphofructokinase; LDHA, lactate dehydrogenase A; NRF1, nuclear respiratory factor 1; TFAM, mitochondrial transcription factor A; CPT1, carnitine palmitoyltransferase 1; CACT, carnitine–acylcarnitine translocase; PINK1, PTEN-induced kinase 1; MIEFs, mitochondrial elongation factors (MIEF1/2); Mfn1/2, mitofusin 1/2; OPA1, optic atrophy 1; HO-1, heme oxygenase-1; GSH, glutathione; GPX, glutathione peroxidase; SOD2, superoxide dismutase 2; AN, animal studies; IV, in vitro or cellular studies; MECH, mechanistic studies;D, direct relevance to aviation; IND, indirect relevance to aviation. Evidence interpretation: The evidence classification distinguishes the source of evidence, study design or evidential role, and direct relevance to aviation. These dimensions are not interchangeable. Observational studies in aviation personnel may provide direct operational context but do not necessarily establish causality. Controlled experiments in other human populations may provide experimental evidence for specific physiological responses, although their applicability to aviation personnel requires separate evaluation. Animal and in vitro studies provide complementary mechanistic insights, whereas computational analyses support hypothesis generation and prioritization. The inclusion of a pathway indicates its potential relevance to the proposed framework and does not, by itself, establish a causal role in flight fatigue. Abbreviations for evidence sources, study designs, and aviation relevance are defined in the table legend.

4.2. Neuroinflammatory Pathways and Key Targets

Neuroinflammation has been implicated in several forms of fatigue-related functional impairment, although the strength and direct relevance of the evidence vary across research settings. Animal studies have implicated microglia-mediated inflammatory signaling and synaptic remodeling in some behavioral consequences of sleep deprivation [100]. These findings suggest potential mechanisms linking sleep loss to altered neural function, but their relevance to fatigue-related changes in aviation personnel remains to be established. Evidence from other clinical populations indicates that NF-κB-mediated expression of pro-inflammatory mediators, including IL-1β and TNF-α, is associated with impaired synaptic plasticity and cognitive dysfunction [101]. Mechanistic studies further suggest that the NLRP3 inflammasome may act as an inflammatory amplification node, promoting the maturation and release of IL-1β under chronic stress [102]. Overall, NF-κB and NLRP3-related inflammatory pathways influence neural network stability through the regulation of inflammatory signaling cascades and

are closely associated with fatigue phenotypes such as impaired vigilance maintenance, reduced cognitive efficiency, and emotional dysregulation (Table 2).

Table 2. Key Neuroinflammatory Pathways and Their Relevance to Flight Fatigue.

Pathway Category	Specific Pathway	Key Targets	Potential Relevance to Fatigue Regulation	Major Associated Scenarios	Major Fatigue Phenotypes	Evidence Base (Source/Design/Aviation Relevance)
Inflammatory signaling regulation	NF-κB signaling pathway [101]	NF-κB, IL-1β, IκBα, TLR4	Modulation of inflammatory signaling	Sleep deprivation, noise, psychological stress	Neurocognitive impairment	OH/OBS/IND
	Pro-inflammatory cytokine signaling [103]	IL-1β, TNF-α	Potential regulation of pro-inflammatory cytokine responses	Psychological stress, high workload	Emotional dysregulation	Review/Review/IND
Inflammatory amplification module	NOD-like receptor signaling pathway [102]	NLRP3, ASC, Caspase-1	Potential modulation of inflammasome activity	Chronic stress, sleep deprivation	Central fatigue, impaired vigilance maintenance	Review/Review/IND

Abbreviations: NF-κB, nuclear factor kappa B; IL-1β, interleukin-1 beta; IκBα, inhibitor of nuclear factor kappa B alpha; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor-alpha; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; Caspase-1, cysteine-aspartic protease-1; OH, other human populations; OBS, observational or associative studies; IND, indirect relevance to aviation.

4.3. Neuroendocrine Regulatory Pathways and Key Targets

The hypothalamic–pituitary–adrenal (HPA) axis is a major neuroendocrine system involved in physiological responses to psychological stress and cognitive workload. Alterations in HPA-axis activity have been implicated in stress-related cognitive and emotional changes and may contribute to fatigue-related functional impairment under sustained operational demands. Stressors such as sustained psychological stress, high task demands, and noise exposure may activate corticotropin-releasing hormone (CRH)-related signaling pathways and promote CRH secretion [104]. Mechanistic and experimental studies suggest that sustained HPA-axis activation and glucocorticoid receptor signaling can influence prefrontal and hippocampal function and may affect neural plasticity and cognitive regulation [105,106]. The extent to which these mechanisms contribute to flight fatigue in aviation personnel requires further direct investigation. Consequently, HPA-axis-related pathways regulate hormonal release and feedback processes and may be associated with changes in cognitive performance and emotional regulation under sustained stress. Their effects are likely to depend on the intensity and duration of stress exposure, the physiological context, and the integrity of feedback regulation (Table 3).

Table 3. Key Neuroendocrine Pathways and Their Relevance to Flight Fatigue.

Pathway Category	Specific Pathway	Key Targets	Potential Relevance to Fatigue Regulation	Major Associated Scenarios	Major Fatigue Phenotypes	Evidence Base (Source/Design/Aviation Relevance)
HPA axis activation	CRH signaling pathway [104]	CRHR1	Regulation of stress-response signaling	Psychological stress, high workload	Cognitive instability	Review/Review/IND

Hormonal effector pathways	Cortisol signaling pathway [107]	GR	Regulation of glucocorticoid signaling	Chronic stress	Emotional fluctuations	AN/MECH/IND
	Glucocorticoid receptor signaling pathway [105,108]	CREB, GR	Potential modulation of receptor-mediated responses	Chronic stress	Emotional and cognitive impairment	Review/Review/IND
Neurotrophic regulation	Neurotrophin signaling pathway [109]	NGF, TrkA, BDNF, TrkB	Potential support of neuroplasticity	Noise exposure, chronic stress	Impaired executive function	Review/Review/IND

Abbreviations: CRHR1, corticotropin-releasing hormone receptor 1; GR, glucocorticoid receptor; CREB, cAMP response element-binding protein; NGF, nerve growth factor; TrkA, tropomyosin receptor kinase A; BDNF, brain-derived neurotrophic factor; TrkB, tropomyosin receptor kinase B; AN, animal studies; IV, in vitro or cellular studies; MECH, mechanistic studies; IND, indirect relevance to aviation.

4.4. Arousal and Circadian Regulatory Pathways and Key Targets

Arousal regulation and the circadian rhythm system constitute core neural regulatory networks responsible for maintaining vigilance and cognitive stability and are particularly important under conditions of sleep deprivation and transmeridian flight. Mechanistic studies have established that the CLOCK–BMAL1 complex regulates the expression of PER and CRY genes through a transcriptional feedback loop that contributes to circadian rhythmicity [110]. Aviation-related human studies separately document circadian misalignment and sleep-related disturbances in flight personnel [10]. In animal models, orexin signaling has been implicated in vigilance maintenance and attentional stability through modulation of wakefulness-related neurotransmitter systems [111]. Overall, circadian rhythm and arousal regulatory pathways support the regulation of vigilance and sleep–wake timing through molecular clock oscillations and arousal signaling, and may be relevant to fatigue-related phenotypes such as impaired vigilance and circadian-related cognitive fluctuations (Table 4).

Table 4. Key Arousal and Circadian Pathways and Their Relevance to Flight Fatigue.

Pathway Category	Specific Pathway	Key Targets	Potential Relevance to Fatigue Regulation	Major Associated Scenarios	Major Fatigue Phenotypes	Evidence Base (Source/Design/Aviation Relevance)
Core molecular clock regulation	circadian rhythm pathway [110]	CLOCK, BMAL1, PER, CRY	Regulation of circadian homeostasis	Transmeridian flight, sleep deprivation	Impaired physiological homeostasis, cognitive fluctuation	Review/Review/IND
Circadian output regulation	Melatonin signaling pathway [112]	MT1, MT2	Regulation of sleep–wake timing	Circadian disruption, sleep deprivation	Impaired working memory, reduced vigilance	Review/Review/IND
Awakening maintains regulation	Orexin signaling pathway [111]	OX1R, OX2R	Regulation of wakefulness and arousal	Sleep deprivation	Attentional instability	AN/MECH/IND

Abbreviations: CLOCK, circadian locomotor output cycles kaput; BMAL1, brain and muscle ARNT-like protein 1; PER, period circadian regulator; CRY, cryptochrome; MT1, melatonin receptor 1

(MTNR1A); MT2, melatonin receptor 2 (MTNR1B); OX1R, orexin receptor type 1; OX2R, orexin receptor type 2; AN, animal studies; MECH, mechanistic studies; IND, indirect relevance to aviation.

4.5. Neurovascular and Cerebral Perfusion Regulatory Pathways and Key Targets

Neurovascular regulation and cerebral perfusion homeostasis are essential for maintaining stable brain function and consciousness, particularly under conditions of high-G exposure, hypoxia, and rapid environmental changes. Cerebral perfusion is regulated by multiple interacting physiological processes. Under hypoxic conditions, stabilization of HIF-1α can promote the expression of genes involved in angiogenesis and metabolic adaptation, thereby supporting tissue-level adaptation to reduced oxygen availability. Research on military aviation and hypoxic responses has highlighted the physiological importance of adaptation to reduced oxygen availability, including pathways involving HIF-1α [113,114]. Mechanistically, hypoxia-induced HIF-1α stabilization promotes the expression of genes involved in angiogenesis and metabolic adaptation, although the extent to which these responses support cerebral function depends on the tissue and physiological context. In addition, mechanistic studies indicate that endothelial nitric oxide synthase (eNOS) participates in the dynamic regulation of cerebral blood flow and neurovascular coupling through modulation of nitric oxide (NO) production [115]. Overall, hypoxia-adaptation and vasodilation-related pathways participate in the regulation of cerebral blood flow and vascular reactivity, providing a plausible physiological link to fatigue-related outcomes such as impaired consciousness and reduced cognitive efficiency under hypoxic or high-G conditions (Table 5).

Table 5. Key Neurovascular Pathways and Their Relevance to Flight Fatigue.

Pathway Category	Specific Pathway	Key Targets	Potential Relevance to Fatigue Regulation	Major Associated Scenarios	Major Fatigue Phenotypes	Evidence Base (Source/Design/Aviation Relevance)
Hypoxia adaptation regulation	HIF-1 signaling pathway [114]	HIF-1α, VEGF, GLUT1	Potential modulation of hypoxic adaptation	Hypoxia	Cognitive impairment, reduced endurance	AP/Review/D
Vasodilatory regulation	Nitric oxide signaling pathway [115]	eNOS	Regulation of vascular tone and vasodilation	High-G exposure; hypoxia	Impaired executive function and working memory	Review/Review/IND

Abbreviations: HIF-1α, hypoxia-inducible factor 1-alpha; VEGF, vascular endothelial growth factor; GLUT1, glucose transporter 1; eNOS, endothelial nitric oxide synthase; AP, aviation personnel (e.g., pilots or aircrew); D, direct relevance to aviation; IND, indirect relevance to aviation.

Beyond their individual roles, these pathways interact to coordinate metabolic homeostasis, inflammatory responses, and adaptation to environmental stress. AMPK, SIRT1, and PGC-1α form an interconnected regulatory axis involved in cellular energy sensing and mitochondrial function. This axis also interacts with NF-κB-mediated inflammatory signaling: SIRT1 can suppress NF-κB activity through deacetylation of its p65 subunit, whereas sustained NF-κB activation may impair SIRT1-associated metabolic regulation, linking inflammatory responses with energy imbalance [116,117]. In addition, hypoxia-inducible factor 1α (HIF-1α) and the core circadian clock components CLOCK/BMAL1 exhibit bidirectional crosstalk, through which hypoxic signaling can influence clock-gene expression and circadian regulation can modulate hypoxic response [118,119]. These interactions suggest that metabolic, inflammatory, and circadian disturbances may overlap under flight-related stress conditions. However, the supporting evidence is largely derived from non-aviation experimental settings, and the contribution of these interactions to flight fatigue remains to be established.

4.6. Scenario–Phenotype–Pathway/Target Framework for Characterizing Flight Fatigue

Taken together, flight-related stressors may be associated with characteristic patterns of functional alterations involving energy metabolism, neuroinflammation, neuroendocrine regulation, circadian rhythm regulation, and cerebral perfusion. Evidence from aviation-related studies and other relevant research suggests that several biological pathways and regulatory targets may contribute to these processes, although the strength and direct applicability of the evidence vary across pathways and study settings.

By integrating operational stress scenarios, observable functional phenotypes, and potentially relevant biological regulatory processes, we propose a Scenario–Phenotype–Pathway/Target (SPT) framework for characterizing flight fatigue (Figure 1). The framework begins with typical operational stress scenarios, links them to corresponding functional phenotypes, and further maps these phenotypes to potentially relevant biological pathways and key regulatory targets. This approach provides a structured means of organizing current evidence and examining the potential biological heterogeneity of flight fatigue.

The SPT framework emphasizes a scenario-driven perspective in which functional phenotypes are considered in relation to their operational contexts and potential biological underpinnings. By organizing the relationships among operational stressors, phenotypic manifestations, and pathway/target-level mechanisms, the framework may help identify research priorities and generate hypotheses for targeted fatigue assessment and intervention. The proposed relationships should therefore be interpreted in accordance with the strength and direct relevance of the supporting evidence.

Importantly, the SPT framework should be interpreted as a conceptual and evidence-informed structure for organizing relationships among flight-related stress scenarios, fatigue phenotypes, and potentially relevant biological pathways and molecular targets. It does not currently constitute a validated predictive model, nor does it establish causal relationships between specific aviation stressors and molecular alterations. Rather, it provides a structured basis for hypothesis generation, evidence integration, and the design of future validation studies. Establishing its predictive or explanatory validity will require aviation-specific datasets, standardized phenotype definitions, and independent computational or experimental validation.

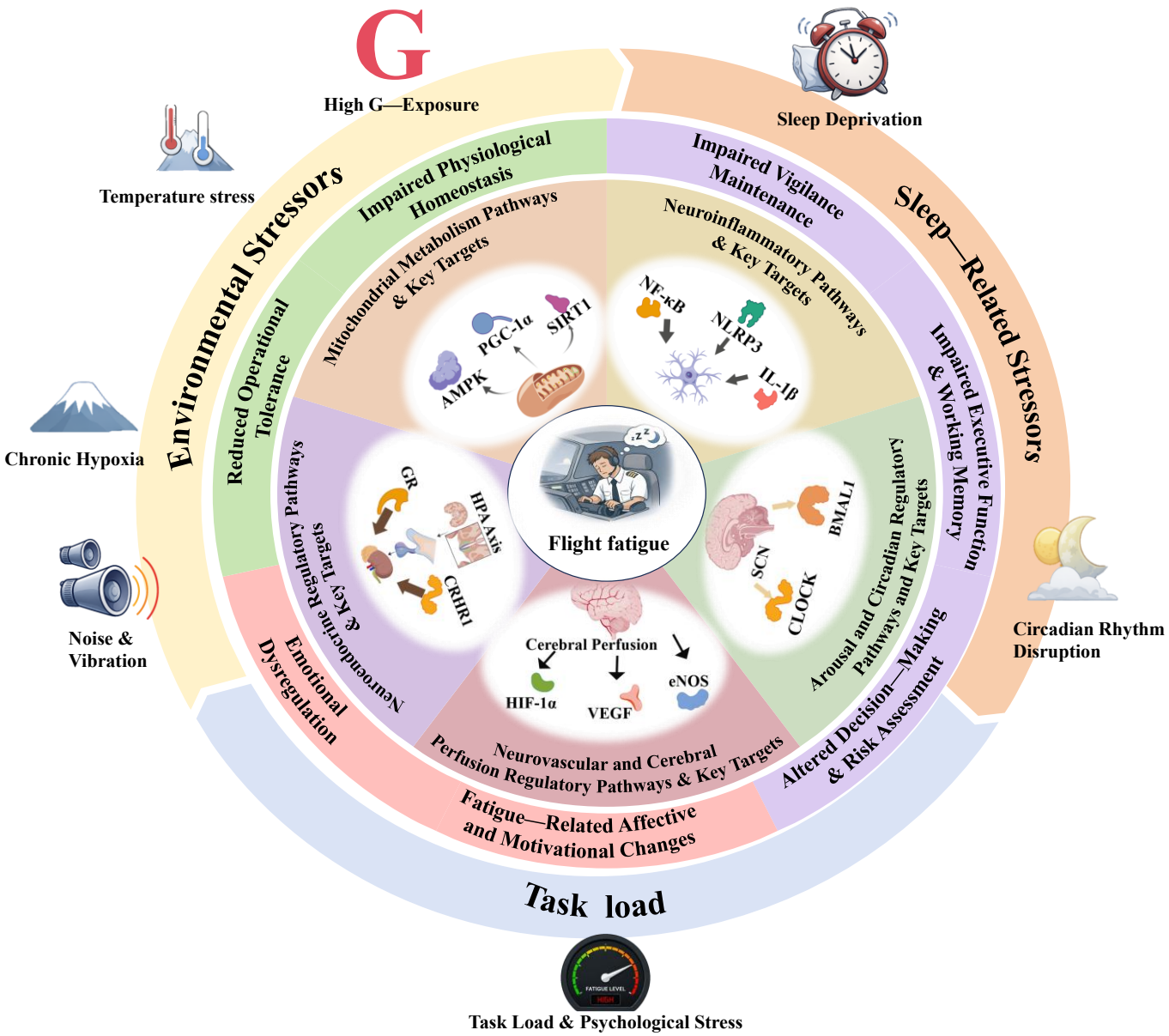

Figure 1. Flight fatigue Scenario–Phenotype–Pathway/Target Framework. This figure illustrates the proposed SPT framework of flight fatigue, integrating flight-related stress exposures, fatigue phenotypes, and their underlying biological mechanisms. The outer layer represents the major stressors encountered during flight operations, including sleep-related stressors, environmental stressors, and task workload. The middle layer summarizes the principal fatigue phenotypes, including reduced physiological tolerance, neurocognitive impairment, and compromised psychological and emotional regulation. The inner layer depicts the key regulatory pathways and targets associated with these phenotypes, encompassing mitochondrial energy metabolism, neuroinflammatory signaling, neuroendocrine regulation, circadian rhythm regulation, and neurovascular and cerebral perfusion pathways. Together, these components provide a conceptual framework for organizing evidence on flight fatigue and identifying potentially relevant intervention targets. The figure was created using Microsoft PowerPoint (Microsoft Office Home 2024). Some graphical elements were created with BioGDP (BioGDP—Generic Diagramming Platform for Biomedical Graphics, https://biogdp.com/zh/workspace) [120]. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; SIRT1, sirtuin 1; NF-κB, nuclear factor kappa B; NLRP3, NOD-,

LRR- and pyrin domain-containing protein 3; IL-1β, interleukin-1 beta; BMAL1, brain and muscle ARNT-like protein 1; CLOCK, circadian locomotor output cycles kaput; HIF-1α, hypoxia-inducible factor 1-alpha; VEGF, vascular endothelial growth factor; eNOS, endothelial nitric oxide synthase; CRHR1, corticotropin-releasing hormone receptor 1; GR, glucocorticoid receptor; HPA, hypothalamic–pituitary–adrenal, SCN, suprachiasmatic nucleus.

5. Flight Fatigue Intervention Strategies

In recent years, research on interventions for flight fatigue has increased steadily. Overall, current anti-fatigue approaches can be divided into two main categories: pharmacological interventions and non-pharmacological interventions. The former primarily acts on neurotransmitters, energy metabolism, or circadian rhythm pathways, while the latter reduces fatigue risk by regulating behavior patterns, operational environments, and psychological states. Additionally, emerging multi-target research methods based on network pharmacology provide a new approach for integrating multiple regulatory pathways.

5.1. Pharmacological and Nutritional Interventions

Pharmacological and nutritional interventions may influence fatigue-related outcomes through effects on neurotransmitter systems, circadian regulation, and energy metabolism. Their onset and duration of action vary across interventions and depend on the physiological processes targeted.

Pharmacological interventions such as caffeine and modafinil rapidly enhance alertness and cognitive performance by blocking adenosine receptors or activating arousal systems, though they may cause tolerance, side effects, or subsequent sleep disruption [121]. Short-acting hypnotics (e.g., zolpidem) are sometimes used to improve sleep quality and indirectly relieve fatigue, but long-term use carries dependency risks [122]. Melatonin supplementation can help synchronize circadian rhythms, but efficacy varies with dosage and individual differences [123]. Additionally, traditional Chinese medicine formulations aimed at Qi and blood supplementation have shown some anti-fatigue effects in certain studies, though mechanisms and clinical evidence in flight populations remain limited [124].

Mitochondria-targeted interventions have attracted attention in recent years. Mitochondrial nutrients are typically small molecules that enhance oxidative phosphorylation efficiency, maintain redox homeostasis, and promote substrate utilization, thereby improving cellular energy metabolism [125]. One such example is Coenzyme Q10 (CoQ10), a key electron carrier in the respiratory chain with antioxidant properties [126,127]. L-carnitine mediates transport of long-chain fatty acids into mitochondria for β-oxidation, enhancing lipid-derived energy and reducing acyl-CoA accumulation [128,129]. Although these compounds participate in different aspects of mitochondrial metabolism and redox regulation, their effects on fatigue-related outcomes may vary according to the compound, dose, population, and experimental context. Their proposed roles in supporting energy metabolism provide a rationale for further investigation (Table 6).

Table 6. Summary of Pharmacological and Nutritional Strategies for Flight Fatigue

Intervention Type	Specific Measure	Main Mechanism	Limitations	Evidence Base (Source/Design/Aviation Relevance)	Notes
Pharmacological	Caffeine [3]	Adenosine receptor blockade, enhanced arousal drive	Tolerance, sleep disruption	AP/Review/D	Systematic review of military pilots
	Modafinil [121]	Activates arousal system, increases dopamine signaling	Requires careful side-effect management	AP/CTRL/D	Air Force RCT
	Short-acting hypnotics (e.g., Zolpidem) [122]	Enhances GABAergic inhibition	Dependency risk	OH/OBS/IND	Meta-analysis of RCT
	Melatonin [123]	Regulates SCN circadian signals	Sensitive to dose and timing	Review/Review/IND	/
	TCM (e.g., Qi and blood tonic formulations [124])	Antioxidant and anti-inflammatory	Mostly animal studies	AN/MECH/IND	Mouse study
Mitochondrial nutrient intervention	Coenzyme Q10 [127]	Enhances mitochondrial ATP production, antioxidant	Mostly short-term studies	Review/Review/IND	Meta-Analysis of RCT
	L-Carnitine [128]	Facilitates fatty acid transport into mitochondria, boosts β-oxidation	Limited effect in healthy individuals	Review/Review/IND	/

Abbreviations: ATP, adenosine triphosphate; GABA, gamma-aminobutyric acid; NADH, reduced nicotinamide adenine dinucleotide; PVT, psychomotor vigilance test; ROS, reactive oxygen species; SCN, suprachiasmatic nucleus; TCM, traditional Chinese medicine; AP, aviation personnel (e.g., pilots or aircrew); AS, aviation-related experimental or simulated settings; OH, other human populations; AN, animal studies; IV, in vitro or cellular studies; CP, computational analyses; OBS, observational or associative studies; CTRL, controlled experiments; MECH, mechanistic studies; PRED, predictive or computational analyses; D, direct relevance to aviation; AR, aviation-related relevance without direct evidence from pilots or aircrew; IND, indirect relevance to aviation; RCT, Randomized Controlled Trial; RCT, Randomized Controlled Trials. Evidence interpretation: The evidence classification distinguishes the source of evidence, study design or evidential role, and direct relevance to aviation. These dimensions are not interchangeable. Observational studies in aviation personnel may provide direct operational context but do not necessarily establish causality. Controlled experiments in other human populations may provide experimental evidence for specific physiological responses, although their applicability to aviation personnel requires separate evaluation. Animal and in vitro studies provide complementary mechanistic insights, whereas computational analyses support hypothesis generation and prioritization. The inclusion of a pathway indicates its potential relevance to the proposed framework and does not, by itself, establish a causal role in flight fatigue. Abbreviations for evidence sources, study designs, and aviation relevance are defined in the table legend.

5.2. Behavioral and Environmental Interventions

Behavioral and Environmental Interventions are applied strategies for managing flight fatigue. They mainly work by regulating behavior patterns, operational environments, and physiological and psychological states, thereby improving fatigue-related functional performance. Behavioral and environmental interventions may offer

practical options for fatigue-risk management, particularly when integrated into established operational procedures. However, their effectiveness, feasibility, and safety depend on the specific intervention, implementation conditions, and operational context.

Behavioral interventions such as strategic naps and sleep extension can reduce adenosine accumulation and restore arousal drive, improving alertness and sustained attention, though their effectiveness is limited by sleep inertia and task context [130]. In terms of environmental management, light therapy and darkness management regulate the circadian system and melatonin secretion, stabilizing sleep rhythms, but their effects depend on lighting parameters and environmental conditions [131]. Some studies have also proposed oxygen supply optimization strategies to improve brain oxygenation, enhancing cognitive stability and circadian recovery [132].

Additionally, physiological interventions such as acupuncture [133] and psychological interventions such as mindfulness training [134] have gained attention in recent years. These may improve sleep quality and subjective fatigue by modulating neuroendocrine function, enhancing circulation, or reducing psychological stress. However, most non-pharmacological interventions remain single-measure approaches, and their effectiveness is often influenced by individual differences and implementation conditions (Table 7).

Table 7. Summary of Behavioral and Environmental Strategies for Flight Fatigue.

Intervention Type	Specific Measure	Main Mechanism	Limitations	Evidence Base (Source/Design/Aviation Relevance)	Notes
Behavioral intervention	Strategic nap [130]	Reduces adenosine accumulation, restores arousal network function	Subject to sleep inertia; effect depends on circadian phase	AP/OBS/D	Observational field study
	Sleep extension [135]	Restores sleep, stabilizes arousal drive	Difficult to implement during high-intensity tasks	OH/CTRL/IND	Ice-hockey RCT
	Attention training/cognitive intervention [136]	Enhances executive control and cognitive tolerance	Limited effect on acute fatigue	OH/CTRL/IND	RCT (59 acquired-brain-injury patients)
	Jet-lag adaptation plans [137]	Resynchronizes circadian rhythms	Significant inter-individual variability	CP/PRED/IND	Computational
	Light exercise/stretching [138]	Improves circulation and oxygen delivery	Limited effect during acute fatigue	Review/Review/IND	Meta-analysis of RCT
Environmental intervention	Light therapy [131]	Modulates CLOCK–BMAL1 circadian system	The effect is dependent on light duration and intensity	OH/CTRL/IND	Parkinson's disease RCT
	Darkness management [139]	Promotes melatonin secretion	Limited by environmental conditions	OH/CTRL/IND	Human controlled experiment (72

					participants)
	Oxygen supply optimization [132]	Enhances brain oxygenation	Limited supporting data	AP/CTRL/AR	Aircrew RCT (not routine pilots)
Physiological intervention	Acupuncture [133]	Modulates neuroendocrine and inflammatory responses	Mostly non-flight populations	Review/Review/IND	Meta-analysis of 4 RCTs; post-stroke
Psychological intervention	Cognitive behavioral therapy [134]	Reduces psychological stress and fatigue perception	Limited supporting data	Review/Review/IND	Meta-analysis

Abbreviations: BMAL1, brain and muscle ARNT-like protein 1; CLOCK, circadian locomotor output cycles kaput;AP, aviation personnel (e.g., pilots or aircrew); OH, other human populations; CP, computational analyses; OBS, observational or associative studies; CTRL, controlled experiments;PRED, predictive or computational analyses; D, direct relevance to aviation; AR, aviation-related relevance without direct evidence from pilots or aircrew; IND, indirect relevance to aviation; RCT, Randomized Controlled Trial.

5.3. Network Pharmacology as a Systems-Level Framework for Multi-Target Anti-Fatigue Formulation Development

Flight fatigue is a multifactorial, non-pathological syndrome involving multiple interacting biological pathways and molecular targets. Consequently, multi-component natural products, particularly herbal formulations, have attracted increasing attention because they may simultaneously modulate multiple biological processes associated with fatigue. However, the complexity of their chemical composition and mechanisms of action presents considerable challenges for conventional pharmacological investigation. In this context, network pharmacology has emerged as a systems-level framework for identifying promising natural products, elucidating multi-target mechanisms, and guiding the rational design and optimization of anti-fatigue formulations [140–143]. Its application to flight fatigue may help prioritize candidate compounds and formulations by integrating fatigue-related phenotypes, molecular targets, and biological pathways. However, the relevance of the resulting predictions depends on the quality of the underlying data and the extent to which the selected targets are supported by evidence relevant to aviation.

In recent years, network pharmacology has been increasingly applied to the screening and optimization of natural product formulations. Representative frameworks, such as Traditional Chinese Medicine Formula Prediction (TCMFP), integrate disease networks, natural product databases, and network topology analysis to establish a systematic workflow from disease target identification to candidate formulation prediction, providing a new paradigm for the rational design of anti-fatigue formulations [144].

A typical workflow begins with the identification of disease-associated targets through literature mining and public databases, including GeneCards, OMIM, and DisGeNET. Target selection should be guided by predefined inclusion criteria and the relevance of each target to the fatigue-related phenotypes and pathways under investigation. These targets are subsequently mapped onto protein–protein interaction (PPI) networks constructed using STRING, where network topology algorithms, such as Degree centrality and PageRank, are applied to prioritize key disease targets. The prioritized targets are then integrated with natural product databases, including TCMSP

and HERB, to construct multilayer target–compound–herb association networks, enabling systematic mapping between disease targets and natural product resources. Finally, candidate formulations may be ranked using predefined criteria that consider target coverage and network characteristics. The data sources, target-mapping procedures, scoring criteria, and prioritization thresholds should be reported transparently to facilitate reproducibility [144,145].

The predicted formulations are typically subjected to further validation through functional enrichment analyses, including Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses, as well as molecular docking to explore potential compound–target interactions. Enrichment analyses identify biological processes and pathways overrepresented among selected targets, whereas molecular docking provides computational evidence regarding the plausibility of selected compound–target interactions. Neither approach independently demonstrates pathway activation or inhibition, direct target engagement, or pharmacological efficacy [143]. Subsequently, animal experiments are conducted to evaluate the effects of candidate formulations on fatigue-related behavioral performance and key molecular pathways, thereby establishing a complete workflow encompassing computational prediction, mechanistic analysis, and experimental validation (Figure 2).

Despite its potential, network pharmacology has several limitations. First, public databases differ in coverage and update frequency, while predicted compound–target associations may not reflect the actual composition, bioavailability, metabolism, or target engagement of a formulation in vivo. Second, network topology measures depend on the structure and completeness of the underlying interaction network; highly connected targets are not necessarily causal drivers of fatigue or the most effective intervention targets. Finally, the biological relevance of predictions based on general fatigue or preclinical models may not fully translate to the complex operational conditions encountered in aviation.

Overall, network pharmacology provides a systems-level approach for prioritizing candidate compounds, targets, and formulations for further investigation. Despite its current limitations, it represents a promising future research direction for the rational screening and optimization of multi-component nutritional formulations targeting fatigue-related pathways, including those potentially relevant to flight fatigue. Further experimental and aviation-specific validation will be essential to establish its translational value.

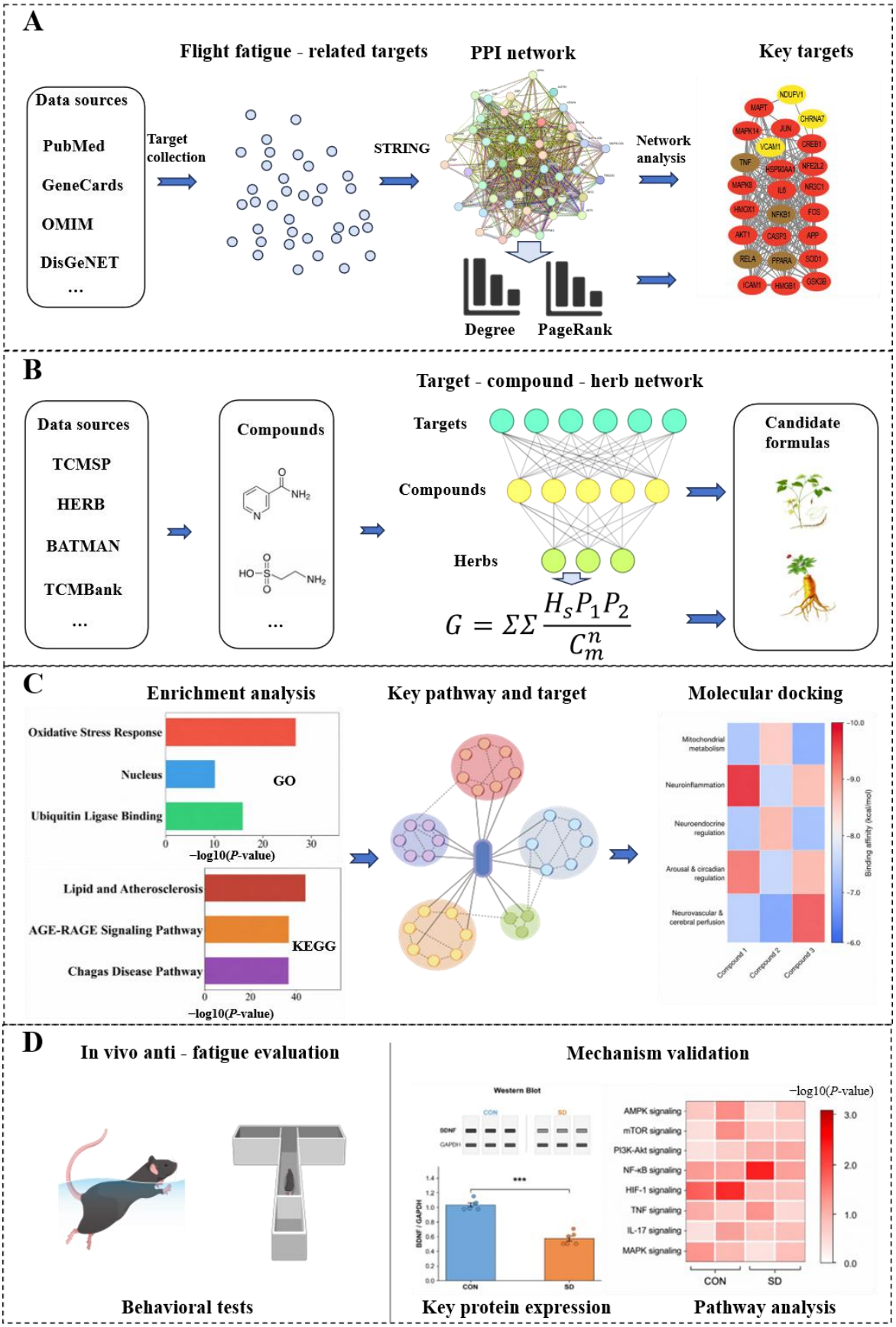

Figure 2. Multi-Target Synergistic Interventions Based on Network Pharmacology. A systems-level workflow for identifying and validating multi-component anti-fatigue formulations using network pharmacology. (**A**) Disease-associated targets are collected from the literature and public databases (e.g., GeneCards, OMIM, and DisGeNET) and projected onto a PPI network constructed using

STRING. Network topology analysis, including Degree centrality or PageRank, is then performed to prioritize key disease targets. "..." represents the remaining flight fatigue data resources. (**B**) The prioritized targets are integrated with natural product databases (e.g., TCMSP, HERBand TCMBank) to construct a multilayer target–compound–herb network. Candidate formulations are subsequently identified through comprehensive scoring and ranking based on network characteristics. Figure 2B – Data sources: "..." represents other available traditional Chinese medicine (TCM) databases. Figure 2B – Compounds: "..." represents the other active compounds identified from TCM herbs. (**C**) Computational validation is performed using functional enrichment analyses (GO and KEGG) and molecular docking to elucidate the potential biological processes, signaling pathways, and compound–target interactions underlying the predicted formulations. (**D**) Experimental validation is conducted in fatigue animal models through behavioral assessments and molecular analyses to verify the anti-fatigue efficacy and elucidate the underlying mechanisms. This workflow provides a systematic framework for the rational discovery, optimization, and validation of multi-target anti-fatigue functional food formulations. The figure was created using Microsoft PowerPoint(Microsoft Office Home 2024). Some graphical elements were created with BioGDP (BioGDP—Generic Diagramming Platform for Biomedical Graphics) [120]. Abbreviations: OMIM, Online Mendelian Inheritance in Man; DisGeNET, Disease Gene Network; PPI, Protein–Protein Interaction; TCMSP, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform; HERB, High-throughput Experiment- and Reference-guided Database of Traditional Chinese Medicine; BATMAN, A Bioinformatics Annotation database for Molecular mechanism; TCMBank, Traditional Chinese Medicine Bank; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; AGE-RAGE, advanced glycation end products–receptor for advanced glycation end products; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; SD, sleep deprivation.

6. Challenges and Opportunities

6.1. Limitations and Evidence Gaps

Despite substantial advances in fatigue research, several limitations remain. Flight fatigue is a multifactorial phenomenon involving physiological, cognitive, and psychological dimensions, yet standardized definitions, phenotype classifications, and assessment criteria remain insufficiently established. In addition, currently available biomarkers have limited specificity for distinguishing different fatigue phenotypes. The evidence base is also heterogeneous, encompassing aviation-specific human studies, other human populations, laboratory-based sleep-deprivation studies, animal models, and in vitro investigations. Although these sources provide complementary insights, the applicability of findings from non-aviation settings to aviation personnel depends on the populations, exposures, and outcomes investigated.

Although several studies have reported changes in oxidative stress-related biomarkers in military pilots and other aviation personnel, the available evidence remains limited by small sample sizes, heterogeneous exposure conditions, and differences in biomarker selection. More importantly, few studies have simultaneously assessed redox-related biomarkers and fatigue-related functional outcomes, making it difficult to determine whether the observed biochemical changes are directly associated with flight fatigue or operational performance impairment.

A further limitation concerns the validation status of the proposed Scenario–Phenotype–Pathway/Target (SPT) framework. The framework provides a conceptual and evidence-informed structure for organizing relationships among flight-related stress scenarios, fatigue phenotypes, and potentially relevant biological pathways and molecular targets. However, it does not yet constitute a validated predictive model, nor does it establish causal relationships between specific aviation stressors and molecular alterations. Its explanatory and predictive validity will require aviation-specific datasets,

standardized phenotype definitions, and independent computational or experimental validation. These limitations define the current scope of the framework and the evidence required to evaluate its applications in fatigue assessment and intervention development.

The evidence summarized in Tables 1–5 and Tables 6–7 also highlights several important gaps. For the biological pathways and molecular targets summarized in Tables 1–5, much of the available evidence is derived from non-aviation populations, preclinical models, or computational analyses, and the extent to which these findings reflect the biological responses of pilots and other aviation personnel remains uncertain. The evidence for interventions summarized in Tables 6 and 7 is similarly heterogeneous in terms of study design, target population, and outcome measures. Consequently, findings from other populations or experimental settings cannot be directly extrapolated to establish efficacy or operational suitability in aviation. Moreover, the proposed links between flight-related scenarios, fatigue phenotypes, and biological pathways have not yet been systematically validated against aviation-specific datasets, and the extent to which the pathways identified can inform effective interventions remains unclear. These gaps underscore the need for standardized outcome measures, more rigorous studies involving aviation personnel, and integrated validation linking mechanistic findings to intervention outcomes under operationally relevant conditions.

6.2. Ethical, Regulatory, and Operational Considerations

The translation of fatigue-monitoring and intervention strategies into aviation practice requires consideration of safety, ethics, regulatory requirements, and operational feasibility. Fatigue assessment systems intended for operational use should be evaluated in relation to their reliability, interpretability, false-alarm rates, and potential consequences for safety-critical decision-making. Predictions generated by biomarkers, wearable devices, or artificial intelligence systems should support, rather than replace, established operational risk-management procedures and professional judgment.

Potential interventions require evaluation of safety, contraindications, individual variability, and compatibility with aviation duties. The operational suitability of pharmacological agents, neuromodulation technologies, and other physiological interventions depends on evidence of efficacy and safety in the intended population and operational context. Their use requires evidence appropriate to the intervention, the intended population, and the operational context, together with compliance with applicable aviation medical and regulatory requirements. A staged evaluation addressing efficacy, safety, human factors, and feasibility under representative flight conditions is therefore important for assessing operational suitability.

6.3. Multimodal Fatigue Monitoring and Personalized Intervention

Advances in wearable sensing technologies, multimodal physiological monitoring, artificial intelligence, and data analytics are creating opportunities for continuous fatigue monitoring, early prediction, and personalized intervention [146–148]. Future systems may integrate behavioral indicators (e.g., reaction time variability), physiological signals (e.g., heart rate variability, respiratory rate, skin temperature, and sleep characteristics), and neurocognitive performance to achieve continuous and multidimensional assessment of fatigue states [149]. When combined with machine learning algorithms, these multimodal data may support the prediction of fatigue progression, the assessment of individual fatigue risk, and the development of phenotype-guided interventions. Emerging wearable intervention technologies, including transcutaneous vagus nerve stimulation [150], transcutaneous electrical acupoint stimulation [151], wearable light therapy [152], and wearable thermal stimulation [153], are being investigated for their potential effects on autonomic regulation, circadian adaptation, cognitive performance,

sleep quality, and physiological recovery. Integrating these technologies with the proposed SPT framework may provide a basis for investigating individualized fatigue management strategies for military aircrew under complex mission conditions.

Author Contributions: J.L., X.L. and Y.K. conceived and supervised the study; R.Z. wrote the first draft; J.L., X.L. and Y.Y. discussed the ideas and contents and edited the manuscript; and R.Z., X.L., Y.Y., F.L. and J.L. edited and finalized the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: This work was supported by the Space Medical Experiment Project of China Manned Space Program (No. HYZHXM01023); a grant from the National Foreign Experts Project (S20250118); and the Key Research and Development Program of Shaanxi (Program No. 2024SF-ZDCYL-03-24).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: During the preparation of this manuscript, the authors used DeepSeek(DeepSeek-V4.1-Flash) for the purposes of language polishing, including grammar correction and improvement of sentence readability. The authors have reviewed and edited the output and take full responsibility for the content of this publication.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. International Civil Aviation Organization. *Fatigue Risk Management Systems: Manual for Regulators*; International Civil Aviation Organization: Montreal, QC, Canada, 2012.
2. Wingelaar-Jagt, Y.Q.; Wingelaar, T.T.; Riedel, W.J.; Ramaekers, J.G. Fatigue in Aviation: Safety Risks, Preventive Strategies and Pharmacological Interventions. *Front. Physiol.* **2021**, *12*, 712628. https://doi.org/10.3389/fphys.2021.712628.
3. Attiah Alzahrani, A.; Alessa, M.F.; Musaad Alharbi, F.; Mohammed Alotaibi, T. Efficacy of Fatigue Countermeasures on Cognitive Performance and Operational Safety in Military Pilots: A Systematic Review. *Cureus* **2025**, *17*, e95823. https://doi.org/10.7759/cureus.95823.
4. Shen, H.; Ren, J.; Shen, H.; Chen, W.; Hua, Z. Experimental Study of Airworthiness Compliance Verification of High-Temperature Environment in Aircraft Cockpit. *Sensors* **2025**, *25*, 764. https://doi.org/10.3390/s25030764.
5. Jordan, J.; Harris, W.C.; Goernert, P.N.; Roberts, J. The Effect of Active Noise Reduction Technology on Noise Induced Pilot Fatigue and Associated Cognitive Performance Decrements. In *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*; Sage Publications: Los Angeles, CA, USA, 1996; Volume 40, pp. 67–71.
6. Oniscenko, B.; Socha, V.; Hanakova, L.; Tlapak, J.; Matowicki, M. Impact of Mild Hypoxia on Pilots' Performance and Physiological Response: A Systematic Review and Experimental Study. *Int. J. Ind. Ergon.* **2024**, *104*, 103650.
7. Sung, J.-Y.; Jeong, D.-H.; Lee, K.-L. Analysis of the Relationship Between Body Imbalance Characteristics and Physical Ability in Air Force Cadets: Physical Function and Gravity Acceleration Resistance. *Sci. Rep.* **2024**, *14*, 19795. https://doi.org/10.1038/s41598-024-70531-2.
8. Lee, M.J.; Yoon, S.; Kim, I.; Sung, J. Effects of Gravitational Acceleration on Physical Fitness, Stress, and Immunity Levels of Prospective Air Force Pilots. *Stress Health* **2025**, *41*, e70060. https://doi.org/10.1002/smi.70060.
9. Naseri, S.; Eslami, R.; Samadi, S.; Hassanlouei, B. Effect of Sleep Deprivation on the Performance of Pilots: A Systematic Review. *Acta Med. Iran.* **2023**, *61*, 709–715.
10. Yang, S.X.; Cheng, S.; Sun, Y.; Tang, X.; Huang, Z. Circadian Disruption in Civilian Airline Pilots. *Aerosp. Med. Hum. Perform.* **2024**, *95*, 381–389. https://doi.org/10.3357/AMHP.6316.2024.
11. Ye, B.; Qin, F.; Zhang, J. Research on Airline Crew Scheduling Model for Fatigue Management. *Aerospace* **2025**, *12*, 1116.
12. Bennett, S.A. Pilot Workload and Fatigue on Four Intra-European Routes: A 12-Month Mixed-Methods Evaluation. *J. Risk Res.* **2019**, *22*, 983–1003.

13. Hamann, A.; Carstengerdes, N. Investigating Mental Workload-Induced Changes in Cortical Oxygenation and Frontal Theta Activity During Simulated Flights. *Sci. Rep.* **2022**, *12*, 6449. https://doi.org/10.1038/s41598-022-10044-y.
14. Shender, B.S. Human Tolerance to Gz Acceleration Loads Generated in High-Performance Helicopters. *Aviat. Space Environ. Med.* **2001**, *72*, 693–703.
15. Cornelissen, S.J.W.M.; Frijters, E.; Gray, G. Lung Function Changes with Acute +Gz Exposure as Assessed by Impulse Oscillometry. *Aerosp. Med. Hum. Perform.* **2025**, *96*, 62–66. https://doi.org/10.3357/AMHP.6433.2024.
16. Akparibo, I.Y.; Anderson, J.; Chumbley, E. Aerospace Gravitational Effects. In *StatPearls*; StatPearls Publishing: Treasure Island, FL, USA, 2023.
17. Keskimölö, T.; Oura, P.; Honkanen, T.; Niinimäki, J.; Sovelius, R.; Leino, T.; Karppinen, J. Association Between Cumulative G-Force Exposure and Cervical Spine Degenerative Changes. *Mil. Med.* **2025**, *190*, e930–e937. https://doi.org/10.1093/milmed/usae452.
18. Saehle, T. Cerebral Hemodynamics During Exposure to Hypergravity (+Gz) or Microgravity (0 G). *Aerosp. Med. Hum. Perform.* **2022**, *93*, 581–592. https://doi.org/10.3357/AMHP.6008.2022.
19. Bogle, J.M.; Benarroch, E.; Sandroni, P. Vestibular-Autonomic Interactions: Beyond Orthostatic Dizziness. *Curr. Opin. Neurol.* **2022**, *35*, 126–134. https://doi.org/10.1097/WCO.0000000000001013.
20. Shen, H.; Hao, M.; Ren, J.; Chen, K.; Gao, Y. Experimental Study on the Effects of Cockpit Noise on Physiological Indicators of Pilots. *Sensors* **2025**, *25*, 4175. https://doi.org/10.3390/s25134175.
21. Smith, S.D. Characterizing the Effects of Airborne Vibration on Human Body Vibration Response. *Aviat. Space Environ. Med.* **2002**, *73*, 36–45.
22. Hahad, O.; Kuntic, M.; Al-Kindi, S.; Kuntic, I.; Gilan, D.; Petrowski, K.; Daiber, A.; Münzel, T. Noise and Mental Health: Evidence, Mechanisms, and Consequences. *J. Expo. Sci. Environ. Epidemiol.* **2025**, *35*, 16–23. https://doi.org/10.1038/s41370-024-00642-5.
23. Arregi, A.; Vegas, O.; Lertxundi, A.; Silva, A.; Ferreira, I.; Bereziartua, A.; Cruz, M.T.; Lertxundi, N. Road Traffic Noise Exposure and Its Impact on Health: Evidence from Animal and Human Studies—Chronic Stress, Inflammation, and Oxidative Stress as Key Components of the Complex Downstream Pathway Underlying Noise-Induced Non-Auditory Health Effects. *Environ. Sci. Pollut. Res.* **2024**, *31*, 46820–46839. https://doi.org/10.1007/s11356-024-33973-9.
24. Jafari, Z.; Kolb, B.E.; Mohajerani, M.H. Chronic Traffic Noise Stress Accelerates Brain Impairment and Cognitive Decline in Mice. *Exp. Neurol.* **2018**, *308*, 1–12. https://doi.org/10.1016/j.expneurol.2018.06.011.
25. Steinman, Y.; Groen, E.; Frings-Dresen, M.H. Exposure to Hypoxia Impairs Helicopter Pilots' Awareness of Environment. *Ergonomics* **2021**, *64*, 1481–1490.
26. Chen, S.; Yao, Q.; Liu, J.; Zhang, X.X.; Du, S.M.; Yu, F.; Zhou, Q.L.; Liu, J. Analysis of papers presented at the 91st Annual Scientific Meeting of the Aerospace Medical Association. *Kongjun Hangkong Yixue (Air Force Aerosp. Med.)* **2022**, *39*, 328–331,352. (In Chinese)
27. Matthys, H. Fit for High Altitude: Are Hypoxic Challenge Tests Useful? *Multidiscip. Respir. Med.* **2011**, *6*, 38. https://doi.org/10.1186/2049-6958-6-1-38.
28. Nishi, S. Effects of Altitude-Related Hypoxia on Aircrews in Aircraft with Unpressurized Cabins. *Mil. Med.* **2011**, *176*, 79–83. https://doi.org/10.7205/MILMED-D-09-00213.
29. Kopp, B.; Bron, D. [Hypoxia in Aviation: List of Possible Causes]. *Ther. Umsch. Rev. Ther.* **2025**, *82*, 192–196. https://doi.org/10.23785/TU.2025.06.004.
30. Kaczmarski, P.; Sochal, M.; Strzelecki, D.; Białasiewicz, P.; Gabryelska, A. Influence of Glutamatergic and GABAergic Neurotransmission on Obstructive Sleep Apnea. *Front. Neurosci.* **2023**, *17*, 1213971. https://doi.org/10.3389/fnins.2023.1213971.
31. Semenza, G.L. Hypoxia-Inducible Factors in Physiology and Medicine. *Cell* **2012**, *148*, 399–408. https://doi.org/10.1016/j.cell.2012.01.021.
32. Peacock, C.A.; Weber, R.; Sanders, G.J.; Seo, Y.; Kean, D.; Pollock, B.S.; Burns, K.J.; Cain, M.; LaScola, P.; Glickman, E.L. Pilot Physiology, Cognition and Flight Performance During Flight Simulation Exposed to a 3810-m Hypoxic Condition. *Int. J. Occup. Saf. Ergon.* **2017**, *23*, 44–49. https://doi.org/10.1080/10803548.2016.1234685.
33. Zhou, B.; Ding, L.; Chen, B.; Shi, H.; Ao, Y.; Xu, R.; Li, Y. Physiological Characteristics and Operational Performance of Pilots in the High Temperature and Humidity Fighter Cockpit Environments. *Sensors* **2021**, *21*, 5798. https://doi.org/10.3390/s21175798.
34. Fredricks, T.R.; Nakazawa, M. Dry Bulb Temperature Effects on Crew Well-Being in Long-Duration Ad Hoc Platform Flights. *Aerosp. Med. Hum. Perform.* **2015**, *86*, 125–130. https://doi.org/10.3357/AMHP.3954.2015.
35. Ao, Y.; Ding, L. Effect of Ambient Temperature and Humidity on Muscle Fatigue of Pilots. *Soc. Occup. Ergon.* **2023**, *106*, 29.

36. Larson, C.; Opichka, M.; McGlynn, M.L.; Collins, C.W.; Slivka, D. Exercise- and Cold-Induced Human PGC-1α mRNA Isoform Specific Responses. *Int. J. Environ. Res. Public Health* **2020**, *17*, 5740. https://doi.org/10.3390/ijerph17165740.
37. Maki, K.A.; Fink, A.M.; Weaver, T.E. Sleep, Time, and Space—Fatigue and Performance Deficits in Pilots, Commercial Truck Drivers, and Astronauts. *SLEEP Adv.* **2022**, *3*, zpac033. https://doi.org/10.1093/sleepadvances/zpac033.
38. O'Hagan, A.D.; Issartel, J.; Wall, A.; Dunne, F.; Boylan, P.; Groeneweg, J.; Herring, M.; Campbell, M.; Warrington, G. "Flying on Empty"–Effects of Sleep Deprivation on Pilot Performance. *Biol. Rhythm Res.* **2020**, *51*, 1133–1154.
39. Rhoads, C.A.; Hagenauer, M.H.; Xiong, J.; Hernandez, E.; Nguyen, D.M.; Saffron, A.; Flandreau, E.I.; Watson, S.; Akil, H. A Meta-Analysis of the Effects of Acute Sleep Deprivation on the Cortical Transcriptome in Rodent Models. *J. Sleep Res.* **2026**, *35*, e70205.
40. Krause, A.J.; Simon, E.B.; Mander, B.A.; Greer, S.M.; Saletin, J.M.; Goldstein-Piekarski, A.N.; Walker, M.P. The Sleep-Deprived Human Brain. *Nat. Rev. Neurosci.* **2017**, *18*, 404–418. https://doi.org/10.1038/nrn.2017.55.
41. Lutz, N.D.; Harkotte, M.; Born, J. Sleep's Contribution to Memory Formation. *Physiol. Rev.* **2026**, *106*, 363–483. https://doi.org/10.1152/physrev.00054.2024.
42. Holst, S.C.; Landolt, H.-P. Sleep-Wake Neurochemistry. *SLEEP Med. Clin.* **2022**, *17*, 151–160. https://doi.org/10.1016/j.jsmc.2022.03.002.
43. Sallinen, M.; Van Dijk, H.; Aeschbach, D.; Maij, A.; Åkerstedt, T. A Large-Scale European Union Study of Aircrew Fatigue During Long Night and Disruptive Duties. *Aerosp. Med. Hum. Perform.* **2020**, *91*, 628–635. https://doi.org/10.3357/AMHP.5561.2020.
44. Gander, P.H.; Mulrine, H.M.; Van Den Berg, M.J.; Smith, A.A.T.; Signal, T.L.; Wu, L.J.; Belenky, G. Effects of Sleep/Wake History and Circadian Phase on Proposed Pilot Fatigue Safety Performance Indicators. *J. Sleep Res.* **2015**, *24*, 110–119. https://doi.org/10.1111/jsr.12197.
45. Stefańska, O.; Barbarska, O.; Minkiewicz-Zochniak, A. Health Implications of Shift Work in Airline Pilots and Cabin Crew: A Narrative Review and Pilot Study Findings. *Nutrients* **2025**, *17*, 3906. https://doi.org/10.3390/nu17243906.
46. Thanuskodi Rajakumar, A.; Kodiveri Muthukaliannan, G. Tuned by Time: The Role of Circadian Rhythms in Metabolic Energy Sensing and Chronotherapy. *Ann. Med.* **2025**, *57*, 2596548. https://doi.org/10.1080/07853890.2025.2596548.
47. Ji, L.; Yi, L.; Li, H.; Han, W.; Zhang, N. Detection of Pilots' Psychological Workload During Turning Phases Using EEG Characteristics. *Sensors* **2024**, *24*, 5176. https://doi.org/10.3390/s24165176.
48. Biernacki, M.P.; Lewkowicz, R. The Role of Visual Conditions and Aircraft Type on Different Aspects of Pilot Workload. *Appl. Ergon.* **2024**, *118*, 104268. https://doi.org/10.1016/j.apergo.2024.104268.
49. Alaimo, A.; Esposito, A.; Orlando, C.; Simoncini, A. Aircraft Pilots Workload Analysis: Heart Rate Variability Objective Measures and NASA-Task Load Index Subjective Evaluation. *Aerospace* **2020**, *7*, 137.
50. Lei, A.A.; Phang, V.W.X.; Lee, Y.Z.; Kow, A.S.F.; Tham, C.L.; Ho, Y.-C.; Lee, M.T. Chronic Stress-Associated Depressive Disorders: The Impact of HPA Axis Dysregulation and Neuroinflammation on the Hippocampus—A Mini Review. *Int. J. Mol. Sci.* **2025**, *26*, 2940. https://doi.org/10.3390/ijms26072940.
51. Alaminos-Torres, A.; Martínez-Álvarez, J.R.; Martínez-Lorca, M.; López-Ejeda, N.; Marrodán Serrano, M.D. Fatigue, Work Overload, and Sleepiness in a Sample of Spanish Commercial Airline Pilots. *Behav. Sci.* **2023**, *13*, 300. https://doi.org/10.3390/bs13040300.
52. Rosa, E.; Lyskov, E.; Grönkvist, M.; Kölegård, R.; Dahlström, N.; Knez, I.; Ljung, R.; Willander, J. Cognitive Performance, Fatigue, Emotional, and Physiological Strains in Simulated Long-Duration Flight Missions. *Mil. Psychol.* **2022**, *34*, 224–236. https://doi.org/10.1080/08995605.2021.1989236.
53. Amann, M.; Venturelli, M.; Ives, S.J.; McDaniel, J.; Layec, G.; Rossman, M.J.; Richardson, R.S. Peripheral Fatigue Limits Endurance Exercise via a Sensory Feedback-Mediated Reduction in Spinal Motoneuronal Output. *J. Appl. Physiol.* **2013**, *115*, 355–364. https://doi.org/10.1152/japplphysiol.00049.2013.
54. Vasquez-Bonilla, A.A.; Yáñez-Sepúlveda, R.; Tuesta, M.; Martin, E.B.-S.; Monsalves-Álvarez, M.; Olivares-Arancibia, J.; Duclos-Bastías, D.; Recabarren-Dueñas, C.; Alacid, F. Acute Fatigue Impairs Heart Rate Variability and Resting Muscle Oxygen Consumption Kinetics. *Appl. Sci.* **2024**, *14*, 9166.
55. Casanova, A.; Wevers, A.; Navarro-Ledesma, S.; Pruimboom, L. Mitochondria: It Is All about Energy. *Front. Physiol.* **2023**, *14*, 1114231. https://doi.org/10.3389/fphys.2023.1114231.
56. Bennett, S.; Tiollier, E.; Owens, D.J.; Brocherie, F.; Louis, J.B. Implications of Heat Stress-Induced Metabolic Alterations for Endurance Training. *Int. J. Sports Med.* **2024**, *45*, 422–435. https://doi.org/10.1055/a-2251-3170.

57. Slungaard, E.; Pollock, R.D.; Stevenson, A.T.; Green, N.D.C.; Newham, D.J.; Harridge, S.D.R. Aircrew Conditioning Programme Impact on +Gz Tolerance. *Aerosp. Med. Hum. Perform.* **2019**, *90*, 764–773. https://doi.org/10.3357/AMHP.5318.2019.
58. Bustamante-Sánchez, A.; Gil-Cabrera, J.; Tornero-Aguilera, J.F.; Fernandez-Lucas, J.; Ramos-Campo, D.J.; Clemente-Suárez, V.J. Effects of Hypoxia on Selected Psychophysiological Stress Responses of Military Aircrew. *BioMed Res. Int.* **2021**, *2021*, 6633851. https://doi.org/10.1155/2021/6633851.
59. Huber, A.; Koenig, J.; Bruns, B.; Bendszus, M.; Friederich, H.-C.; Simon, J.J. Brain Activation and Heart Rate Variability as Markers of Autonomic Function Under Stress. *Sci. Rep.* **2025**, *15*, 28114. https://doi.org/10.1038/s41598-025-12430-8.
60. Agorastos, A.; Mansueto, A.C.; Hager, T.; Pappi, E.; Gardikioti, A.; Stiedl, O. Heart Rate Variability as a Translational Dynamic Biomarker of Altered Autonomic Function in Health and Psychiatric Disease. *Biomedicines* **2023**, *11*, 1591. https://doi.org/10.3390/biomedicines11061591.
61. Liu, H.; Yu, X.; Wang, G.; Han, Y.; Wang, W. Effects of 24-h Acute Total Sleep Deprivation on Physiological Coupling in Healthy Young Adults. *Front. Neurosci.* **2022**, *16*, 952329. https://doi.org/10.3389/fnins.2022.952329.
62. McKenna, Z.J.; Foster, J.; Atkins, W.C.; Belval, L.N.; Watso, J.C.; Jarrard, C.P.; Orth, B.D.; Crandall, C.G. Age Alters the Thermoregulatory Responses to Extreme Heat Exposure with Accompanying Activities of Daily Living. *J. Appl. Physiol. Bethesda Md.* **1985**, *2023*, 135, 445–455. https://doi.org/10.1152/japplphysiol.00285.2023.
63. Hudson, A.N.; Van Dongen, H.P.A.; Honn, K.A. Sleep Deprivation, Vigilant Attention, and Brain Function: A Review. *Neuropsychopharmacology* **2020**, *45*, 21–30. https://doi.org/10.1038/s41386-019-0432-6.
64. Yao, L.; Wang, Y.; Gao, Y.; Gao, H.; Guo, X. The Role of the Fronto-Parietal Network in Modulating Sustained Attention Under Sleep Deprivation: An Functional Magnetic Resonance Imaging Study. *Front. Psychiatry* **2023**, *14*, 1289300. https://doi.org/10.3389/fpsyt.2023.1289300.
65. Yu, J.; Zhou, Y.; Han, X.; Li, Z.; Chen, F.; Zhang, L. Impaired Vigilance in Patients with Narcolepsy Type 1: A Psychomotor Vigilance Task Study. *Nat. Sci. Sleep* **2024**, *16*, 2021–2028. https://doi.org/10.2147/NSS.S491893.
66. Dolev, T.; Maoz, I.; Zubedat, S.; Aga-Mizrachi, S.; Levkovsky, A.; Nakdimon, I.; Ben-Ari, O.; Grinstein, D.; Gordon, B.; Avital, A. Attention Regulation Among Sleep-Deprived Air-Force Pilots. *J. Neurosci. Res.* **2025**, *103*, e70052. https://doi.org/10.1002/jnr.70052.
67. Jones, D.T.; Graff-Radford, J. Executive Dysfunction and the Prefrontal Cortex. *Contin. Minneap. Minn.* **2021**, *27*, 1586–1601. https://doi.org/10.1212/CON.0000000000001009.
68. Wang, X.; Cui, L.; Ji, X. Cognitive Impairment Caused by Hypoxia: From Clinical Evidences to Molecular Mechanisms. *Metab. Brain Dis.* **2022**, *37*, 51–66. https://doi.org/10.1007/s11011-021-00796-3.
69. Zhu, R.; Ma, X.; You, X. The Effect of Working Memory Load on Inattentional Deafness During Aeronautical Decision-Making. *Appl. Ergon.* **2023**, *113*, 104099. https://doi.org/10.1016/j.apergo.2023.104099.
70. Gong, H.; Liu, Y.-X.; Xiaoluo, Q.-L.; Gong, M.-F.; Liu, Z.; Wu, S.-R.; Chen, Z.-Y.; Liu, T.-Y.; Zhao, J.-H.; Wang, L.; et al. Unraveling the Complexity of Cognitive Impairment Following High-Altitude Exposure: From Preclinical Animal Models to Human Organoids. *Front. Neurosci.* **2025**, *19*, 1679858. https://doi.org/10.3389/fnins.2025.1679858.
71. Li, W.; Li, R.; Xie, X.; Chang, Y. Evaluating Mental Workload During Multitasking in Simulated Flight. *Brain Behav.* **2022**, *12*, e2489. https://doi.org/10.1002/brb3.2489.
72. Masi, G.; Amprimo, G.; Ferraris, C.; Priano, L. Stress and Workload Assessment in Aviation—A Narrative Review. *Sensors* **2023**, *23*, 3556. https://doi.org/10.3390/s23073556.
73. Porcelli, A.J.; Delgado, M.R. Acute Stress Modulates Risk Taking in Financial Decision Making. *Psychol. Sci.* **2009**, *20*, 278–283. https://doi.org/10.1111/j.1467-9280.2009.02288.x.
74. Gangopadhyay, P.; Chawla, M.; Dal Monte, O.; Chang, S.W.C. Prefrontal–Amygdala Circuits in Social Decision-Making. *Nat. Neurosci.* **2021**, *24*, 5–18. https://doi.org/10.1038/s41593-020-00738-9.
75. Reale, C.; Salwei, M.E.; Militello, L.G.; Weinger, M.B.; Burden, A.; Sushereba, C.; Torsher, L.C.; Andreae, M.H.; Gaba, D.M.; McIvor, W.R.; et al. Decision-Making During High-Risk Events: A Systematic Literature Review. *J. Cogn. Eng. Decis. Mak.* **2023**, *17*, 188–212. https://doi.org/10.1177/15553434221147415.
76. Flood, A.; Keegan, R.J. Cognitive Resilience to Psychological Stress in Military Personnel. *Front. Psychol.* **2022**, *13*, 809003. https://doi.org/10.3389/fpsyg.2022.809003.
77. Rosa, E.; Gronkvist, M.; Kolegard, R.; Dahlstrom, N.; Knez, I.; Ljung, R.; Willander, J. Fatigue, Emotion, and Cognitive Performance in Simulated Long-Duration, Single-Piloted Flight Missions. *Aerosp. Med. Hum. Perform.* **2021**, *92*, 710–719. https://doi.org/10.3357/AMHP.5798.2021.

78. Velauthapillai, A.; Vonk, M.C.; Van Den Ende, C.H.; Vriezekolk, J.E. Within-Person Fluctuations of Fatigue in Patients with a Clinical Diagnosis of Systemic Sclerosis and Its Relationship with Mood, Pain, Sleep and Physical Activity. *J. Scleroderma Relat. Disord.* **2024**, *9*, 223–232. https://doi.org/10.1177/23971983241242836.
79. Kunasegaran, K.; Ismail, A.M.H.; Ramasamy, S.; Gnanou, J.V.; Caszo, B.A.; Chen, P.L. Understanding Mental Fatigue and Its Detection: A Comparative Analysis of Assessments and Tools. *PeerJ* **2023**, *11*, e15744. https://doi.org/10.7717/peerj.15744.
80. Jansson-Fröjmark, M.; Hossain, S. Emotion Dysregulation in Insomnia Disorder: The Possible Role of Psychiatric Comorbidity. *Front. Sleep* **2024**, *3*, 1383552. https://doi.org/10.3389/frsle.2024.1383552.
81. Chen, P.; Sun, H.-L.; Feng, Y.; Zhang, Q.; Si, T.L.; Su, Z.; Cheung, T.; Ungvari, G.S.; Zhang, E.; Chen, M.; et al. The Association of Sleep Duration and Sleep Quality with Depression and Anxiety Among Chinese Commercial Pilots. *Depress. Anxiety* **2024**, *2024*, 9920975. https://doi.org/10.1155/da/9920975.
82. Billones, R.; Liwang, J.K.; Butler, K.; Graves, L.; Saligan, L.N. Dissecting the Fatigue Experience: A Scoping Review of Fatigue Definitions, Dimensions, and Measures in Non-Oncologic Medical Conditions. *Brain Behav. Immun.-Health* **2021**, *15*, 100266. https://doi.org/10.1016/j.bbih.2021.100266.
83. Chen, L.R.; Wang, P.X.; Wang, Z.; Long, J.G. Mitochondria: Intracellular sensors of space microgravity. *Hangtian Yixue Yu Yixue Gongcheng (Space Med. Med. Eng.)* **2024**, *35*, 258–267. (In Chinese)
84. Wang, K.; Xu, Y.; Sun, Q.; Long, J.; Liu, J.; Ding, J. Mitochondria Regulate Cardiac Contraction Through ATP-Dependent and Independent Mechanisms. *Free Radic. Res.* **2018**, *52*, 1256–1265. https://doi.org/10.1080/10715762.2018.1453137.
85. Shen, Q.; Wu, X.; Huang, C.; Ding, X.; Wan, C. Aerobic Exercise Activates AMPK/PGC-1α Pathway, Inhibits Cardiomyocyte Apoptosis Improves Mitochondrial and Infarcted Heart Function. *Dokl. Biochem. Biophys.* **2024**, *518*, 420–428. https://doi.org/10.1134/S1607672924600556.
86. Gupta, S.; Afzal, M.; Agrawal, N.; Almalki, W.H.; Rana, M.; Gangola, S.; Chinni, S.V.; Kumar, K.B.; Ali, H.; Singh, S.K.; et al. Harnessing the FOXO-SIRT1 Axis: Insights into Cellular Stress, Metabolism, and Aging. *Biogerontology* **2025**, *26*, 65. https://doi.org/10.1007/s10522-025-10207-0.
87. Lou, H.; Yao, J.; Zhang, Y.; Wu, X.; Sun, L.; Wang, Y.; Cong, D. Potential Effect of Acupuncture on Mitochondrial Biogenesis, Energy Metabolism and Oxidation Stress in MCAO Rat via PGC-1α/NRF1/TFAM Pathway. *J. Stroke Cerebrovasc. Dis. Off. J. Natl. Stroke Assoc.* **2024**, *33*, 107636. https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107636.
88. Zhao, X.; Wang, Z.; Wang, L.; Jiang, T.; Dong, D.; Sun, M. The PINK1/Parkin Signaling Pathway-Mediated Mitophagy: A Forgotten Protagonist in Myocardial Ischemia/Reperfusion Injury. *Pharmacol. Res.* **2024**, *209*, 107466. https://doi.org/10.1016/j.phrs.2024.107466.
89. Yu, R.; Liu, T.; Jin, S.-B.; Ankarcrona, M.; Lendahl, U.; Nistér, M.; Zhao, J. MIEF1/2 Orchestrate Mitochondrial Dynamics Through Direct Engagement with Both the Fission and Fusion Machineries. *BMC Biol.* **2021**, *19*, 229. https://doi.org/10.1186/s12915-021-01161-7.
90. Kaplán, P.; Tatarková, Z.; Lichardusová, L.; Kmeťová Sivoňová, M.; Tomašcová, A.; Račay, P.; Lehotský, J. Age-Associated Changes in Antioxidants and Redox Proteins of Rat Heart. *Physiol. Res.* **2019**, *68*, 883–892. https://doi.org/10.33549/physiolres.934170.
91. Sun, Y.-Y.; Zhu, H.-J.; Zhao, R.-Y.; Zhou, S.-Y.; Wang, M.-Q.; Yang, Y.; Guo, Z.-N. Remote Ischemic Conditioning Attenuates Oxidative Stress and Inflammation via the Nrf2/HO-1 Pathway in MCAO Mice. *Redox Biol.* **2023**, *66*, 102852. https://doi.org/10.1016/j.redox.2023.102852.
92. Mailloux, R.J. An Update on Mitochondrial Reactive Oxygen Species Production. *Antioxidants* **2020**, *9*, 472. https://doi.org/10.3390/antiox9060472.
93. Bojahr, J.; Jörres, R.A.; Kronseder, A.; Weber, F.; Ledderhos, C.; Roiu, I.; Karrasch, S.; Nowak, D.; Teupser, D.; Königer, C. Effects of Training Flights of Combat Jet Pilots on Parameters of Airway Function, Diffusing Capacity and Systemic Oxidative Stress, and Their Association with Flight Parameters. Eur. J. Med. Res. 2024, 29, 100, doi:10.1186/s40001-024-01668-z.
94. Petraki, K.; Grammatikopoulou, M.G.; Tekos, F.; Skaperda, Z.; Orfanou, M.; Mesnage, R.; Vassilakou, T.; Kouretas, D. Estimation of Redox Status in Military Pilots during Hypoxic Flight-Simulation Conditions-a Pilot Study. Antioxidants 2022, 11, 1241, doi:10.3390/antiox11071241.
95. Huang, Y.-C.; Wu, S.-Y.; Liao, C.-T.; Huang, W.-W.; Chu, H.; Tu, M.-Y.; Lin, Y.-C.; Lai, C.-Y. Oxidative Stress Response to Simulated Altitude Training: A Longitudinal Study of the Biomarker Variation and the Contributing Factors. BMJ Mil. Health 2026, e003189, doi:10.1136/military-2025-003189.
96. Yang, M.; Lu, Y.; Piao, W.; Jin, H. The Translational Regulation in mTOR Pathway. *Biomolecules* **2022**, *12*, 802. https://doi.org/10.3390/biom12060802.

97. Ramasubbu, K.; Devi Rajeswari, V. Impairment of Insulin Signaling Pathway PI3K/Akt/mTOR and Insulin Resistance Induced AGEs on Diabetes Mellitus and Neurodegenerative Diseases: A Perspective Review. *Mol. Cell. Biochem.* **2023**, *478*, 1307–1324. https://doi.org/10.1007/s11010-022-04587-x.
98. Zhang, J.; Zhang, T.; Song, D.; Xu, D. Targeting Glycolysis in Prostate Cancer: Molecular Mechanisms and Therapeutic Advances. *Biochim. Biophys. Acta BBA-Rev. Cancer* **2026**, *1881*, 189537. https://doi.org/10.1016/j.bbcan.2026.189537.
99. Houten, S.M.; Violante, S.; Ventura, F.V.; Wanders, R.J.A. The Biochemistry and Physiology of Mitochondrial Fatty Acid β-Oxidation and Its Genetic Disorders. *Annu. Rev. Physiol.* **2016**, *78*, 23–44. https://doi.org/10.1146/annurev-physiol-021115-105045.
100. Ni, R.-J.; Yuan, W.-J.; Wang, Y.-Y.; Yang, X.; Wei, J.-X.; Zhao, L.-S.; Wang, Q.; Tang, X.-D.; Ma, X.-H. Microglia-Mediated Inflammation and Synaptic Pruning Contribute to Sleep Deprivation-Induced Mania in a Sex-Specific Manner. *Transl. Psychiatry* **2025**, *15*, 285. https://doi.org/10.1038/s41398-025-03525-x.
101. Li, H.; Chen, W.; Gou, M.; Li, W.; Tong, J.; Zhou, Y.; Xie, T.; Yu, T.; Feng, W.; Li, Y.; et al. The Relationship Between TLR4/NF-κB/IL-1β Signaling, Cognitive Impairment, and White-Matter Integrity in Patients with Stable Chronic Schizophrenia. *Front. Psychiatry* **2022**, *13*, 966657. https://doi.org/10.3389/fpsyt.2022.966657.
102. Li, H.; Guan, Y.; Liang, B.; Ding, P.; Hou, X.; Wei, W.; Ma, Y. Therapeutic Potential of MCC950, a Specific Inhibitor of NLRP3 Inflammasome. *Eur. J. Pharmacol.* **2022**, *928*, 175091. https://doi.org/10.1016/j.ejphar.2022.175091.
103. Tylutka, A.; Walas, Ł.; Zembron-Lacny, A. Level of IL-6, TNF, and IL-1β and Age-Related Diseases: A Systematic Review and Meta-Analysis. *Front. Immunol.* **2024**, *15*, 1330386. https://doi.org/10.3389/fimmu.2024.1330386.
104. Zheng, J.; Yue, N.; Tian, Z.; Yu, J.; Li, B. Beyond the HPA Axis: Synaptic Circuits of PVNCRH Neurons in Stress-Related Psychiatric Disorders. *Pharmacol. Res.* **2026**, *227*, 108179. https://doi.org/10.1016/j.phrs.2026.108179.
105. Su, C.; Huang, T.; Zhang, M.; Zhang, Y.; Zeng, Y.; Chen, X. Glucocorticoid Receptor Signaling in the Brain and Its Involvement in Cognitive Function. *Neural Regen. Res.* **2025**, *20*, 2520–2537. https://doi.org/10.4103/NRR.NRR-D-24-00355.
106. De Alcubierre, D.; Ferrari, D.; Mauro, G.; Isidori, A.M.; Tomlinson, J.W.; Pofi, R. Glucocorticoids and Cognitive Function: A Walkthrough in Endogenous and Exogenous Alterations. *J. Endocrinol. Investig.* **2023**, *46*, 1961–1982. https://doi.org/10.1007/s40618-023-02091-7.
107. Castillo-Ramírez, L.A.; Ryu, S.; De Marco, R.J. Cortisol Dynamics and GR-Dependent Feedback Regulation in Zebrafish Larvae Exposed to Repeated Stress. *Biol. Open* **2024**, *13*, bio061683. https://doi.org/10.1242/bio.061683.
108. Göver, T.; Slezak, M. Targeting Glucocorticoid Receptor Signaling Pathway for Treatment of Stress-Related Brain Disorders. *Pharmacol. Rep.* **2024**, *76*, 1333–1345. https://doi.org/10.1007/s43440-024-00654-w.
109. Liu, H.; Wang, G.; Wang, C.; Hou, D.; Li, S.; Fan, Y.; Liu, B. Neurotrophin NGF/TrkA and BDNF/TrkB Signaling Orchestrates the Immune Microenvironment in Osteosarcoma. *Front. Immunol.* **2026**, *16*, 1727434. https://doi.org/10.3389/fimmu.2025.1727434.
110. Liu, Y.; Sancar, A. Biochemical Mechanism of the Mammalian Circadian Clock. *FEBS Lett.* **2026**, *600*, 716–731. https://doi.org/10.1002/1873-3468.70150.
111. Zhu, X.; Guo, L.; Chen, N.; Wang, L.; Dai, S.; Liu, X.; Chen, X.; Wang, C.; Cao, Y.; Hu, H.; et al. Sleep Fragmentation Exacerbates Myocardial Ischemia-Reperfusion Injury via Hypothalamic Paraventricular Nucleus-Resident OX1R-Mediated Sympathetic Hyperactivity in Adult Mice. *Ann. Med.* **2025**, *57*, 2599059. https://doi.org/10.1080/07853890.2025.2599059.
112. Ding, W.; Xu, Y.; Ding, W.; Tang, Q.; Zhang, B.; Yuan, Y.; Jin, J. Research Progress on Melatonin, 5-HT, and Orexin in Sleep Disorders of Children with Autism Spectrum Disorder. *Biomol. Biomed.* **2024**, *25*, 525–533. https://doi.org/10.17305/bb.2024.11182.
113. Shaw, D.M.; Cabre, G.; Gant, N. Hypoxic Hypoxia and Brain Function in Military Aviation: Basic Physiology and Applied Perspectives. *Front. Physiol.* **2021**, *12*, 665821. https://doi.org/10.3389/fphys.2021.665821.
114. Shaharuddin, S.; Rahman, N.M.A.N.A.; Masarudin, M.J.; Alamassi, M.N. Hif-1 Activation and Inflammatory Responses to Hypoxia. *Int. J. Aviat. Aeronaut. Aerosp.* **2023**, *10*, 3. https://doi.org/10.58940/2374-6793.1798.
115. Scarpellino, G.; Brunetti, V.; Berra-Romani, R.; De Sarro, G.; Guerra, G.; Soda, T.; Moccia, F. The Unexpected Role of the Endothelial Nitric Oxide Synthase at the Neurovascular Unit: Beyond the Regulation of Cerebral Blood Flow. *Int. J. Mol. Sci.* **2024**, *25*, 9071. https://doi.org/10.3390/ijms25169071.
116. Yang, Z.; Kahn, B.B.; Shi, H.; Xue, B. Macrophage A1 AMP-Activated Protein Kinase (α1AMPK) Antagonizes Fatty Acid-Induced Inflammation Through SIRT1. *J. Biol. Chem.* **2010**, *285*, 19051–19059. https://doi.org/10.1074/jbc.M110.123620.
117. Kauppinen, A.; Suuronen, T.; Ojala, J.; Kaarniranta, K.; Salminen, A. Antagonistic Crosstalk Between NF-κB and SIRT1 in the Regulation of Inflammation and Metabolic Disorders. *Cell Signal.* **2013**, *25*, 1939–1948. https://doi.org/10.1016/j.cellsig.2013.06.007.

118. Peek, C.B.; Levine, D.C.; Cedernaes, J.; Taguchi, A.; Kobayashi, Y.; Tsai, S.J.; Bonar, N.A.; McNulty, M.R.; Ramsey, K.M.; Bass, J. Circadian Clock Interaction with HIF1α Mediates Oxygenic Metabolism and Anaerobic Glycolysis in Skeletal Muscle. *Cell Metab.* **2026**, *38*, 1917. https://doi.org/10.1016/j.cmet.2026.07.017.
119. O'Connell, E.J.; Martinez, C.-A.; Liang, Y.G.; Cistulli, P.A.; Cook, K.M. Out of Breath, out of Time: Interactions Between HIF and Circadian Rhythms. *Am. J. Physiol. Cell Physiol.* **2020**, *319*, C533–C540. https://doi.org/10.1152/ajpcell.00305.2020.
120. Jiang, S.; Li, H.; Zhang, L.; Mu, W.; Zhang, Y.; Chen, T.; Wu, J.; Tang, H.; Zheng, S.; Liu, Y.; et al. Generic Diagramming Platform (GDP): A Comprehensive Database of High-Quality Biomedical Graphics. *Nucleic Acids Res.* **2025**, *53*, D1670–D1676. https://doi.org/10.1093/nar/gkae973.
121. Wingelaar-Jagt, Y.Q.; Bottenheft, C.; Riedel, W.J.; Ramaekers, J.G. Effects of Modafinil and Caffeine on Night-Time Vigilance of Air Force Crewmembers: A Randomized Controlled Trial. *J. Psychopharmacol.* **2023**, *37*, 172–180. https://doi.org/10.1177/02698811221142568.
122. Xiang, T.; Cai, Y.; Hong, Z.; Pan, J. Efficacy and Safety of Zolpidem in the Treatment of Insomnia Disorder for One Month: A Meta-Analysis of a Randomized Controlled Trial. *Sleep Med.* **2021**, *87*, 250–256. https://doi.org/10.1016/j.sleep.2021.09.005.
123. Del Casale, A.; Arena, J.F.; Giannetti, F.; Minervino, A.; Biggio, G.; Girardi, P. The Use of Prolonged-Release Melatonin in Circadian Medicine: A Systematic Review. *Minerva Med.* **2024**, *115*, 125–142. https://doi.org/10.23736/S0026-4806.24.09303-0.
124. Chen, H.; Ma, X.; Cao, L.; Zhao, S.; Zhao, C.; Yin, S.; Hu, H. A Multi-Ingredient Formula Ameliorates Exercise-Induced Fatigue by Changing Metabolic Pathways and Increasing Antioxidant Capacity in Mice. *Foods* **2021**, *10*, 3120. https://doi.org/10.3390/foods10123120.
125. Peng, Y.; Gao, P.; Shi, L.; Chen, L.; Liu, J.; Long, J. Central and Peripheral Metabolic Defects Contribute to the Pathogenesis of Alzheimer's Disease: Targeting Mitochondria for Diagnosis and Prevention. *Antioxid. Redox Signal.* **2020**, *32*, 1188–1236. https://doi.org/10.1089/ars.2019.7763.
126. Castro-Marrero, J.; Segundo, M.J.; Lacasa, M.; Martinez-Martinez, A.; Sentañes, R.S.; Alegre-Martin, J. Effect of Dietary Coenzyme Q10 Plus NADH Supplementation on Fatigue Perception and Health-Related Quality of Life in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial. *Nutrients* **2021**, *13*, 2658. https://doi.org/10.3390/nu13082658.
127. Tsai, I.-C.; Hsu, C.-W.; Chang, C.-H.; Tseng, P.-T.; Chang, K.-V. Effectiveness of Coenzyme Q10 Supplementation for Reducing Fatigue: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Front. Pharmacol. 2022, 13, 883251, doi:10.3389/fphar.2022.883251.
128. Xiang, F.; Zhang, Z.; Xie, J.; Xiong, S.; Yang, C.; Liao, D.; Xia, B.; Lin, L. Comprehensive Review of the Expanding Roles of the Carnitine Pool in Metabolic Physiology: Beyond Fatty Acid Oxidation. J. Transl. Med. 2025, 23, 324, doi:10.1186/s12967-025-06341-5.
129. Shen, L.; Li, J.; Chen, Y.; Lu, Z.; Lyu, W. L-Carnitine's Role in KAATSU Training- Induced Neuromuscular Fatigue. Biomed. Pharmacother. Biomedecine Pharmacother. 2020, 125, 109899, doi:10.1016/j.biopha.2020.109899.
130. Hilditch, C.J.; Arsintescu, L.; Pradhan, S.; Gregory, K.B.; Flynn-Evans, E.E. Investigating the Causes and Consequences of Controlled Rest on the Flight Deck. *Front. Environ. Health* **2024**, *3*, 1368628. https://doi.org/10.3389/fenvh.2024.1368628.
131. Feigl, B.; Lewis, S.J.G.; Burr, L.D.; Schweitzer, D.; Gnyawali, S.; Vagenas, D.; Carter, D.D.; Zele, A.J. Efficacy of Biologically-Directed Daylight Therapy on Sleep and Circadian Rhythm in Parkinson's Disease: A Randomised, Double-Blind, Parallel-Group, Active-Controlled, Phase 2 Clinical Trial. *eClinicalMedicine* **2024**, *69*, 102474. https://doi.org/10.1016/j.eclinm.2024.102474.
132. Falla, M.; Van Veelen, M.J.; Falk, M.; Weiss, E.M.; Roveri, G.; Masè, M.; Weber, B.; Randi, A.; Brugger, H.; Hüfner, K.; et al. Effect of Oxygen Supplementation on Cognitive Performance among HEMS Providers after Acute Exposure to Altitude: The HEMS II Randomized Clinical Trial. *Scand. J. Trauma Resusc. Emerg. Med.* **2024**, *32*, 65. https://doi.org/10.1186/s13049-024-01238-6.
133. Jianyu, Y.; Haiyan, L.I.; Dingyi, X.; Mingren, C.; Rixin, C. Efficacy of Acupuncture Therapy for Post-Stroke Fatigue: A Systematic Review and Meta-Analysis. *J. Tradit. Chin. Med. Chung Tsa Chih Ying Wen Pan* **2023**, *43*, 27–33. https://doi.org/10.19852/j.cnki.jtcm.20221006.003.
134. Maas Genannt Bermpohl, F.; Kucharczyk-Bodenburg, A.-C.; Martin, A. Efficacy and Acceptance of Cognitive Behavioral Therapy in Adults with Chronic Fatigue Syndrome: A Meta-Analysis. *Int. J. Behav. Med.* **2024**, *31*, 895–910. https://doi.org/10.1007/s12529-023-10254-2.
135. Varesco, G.; Lavoie, F.; Adoutoro, J.; Michaud, X.; Guloy, S.; Martin, A.; Simonelli, G. Acute Effects of Sleep Extension on Fatigue, Inhibitory Control, Short-Term Vigilance and Neuromuscular Function in Youth Elite Ice Hockey Players: A Randomised Crossover Trial. *J. Sleep Res.* **2025**, *35*, e70269. https://doi.org/10.1111/jsr.70269.

136. Holmqvist, A.; Bartfai, A.; Markovic, G.; Möller, M.C. Does Intensive Training of Attention Influence Cognitive Fatigability in Patients with Acquired Brain Injury? *Front. Neurosci.* **2021**, *15*, 656876. https://doi.org/10.3389/fnins.2021.656876.
137. Li, Y.; Androulakis, I.P. Light Entrainment of the SCN Circadian Clock and Implications for Personalized Alterations of Corticosterone Rhythms in Shift Work and Jet Lag. *Sci. Rep.* **2021**, *11*, 17929. https://doi.org/10.1038/s41598-021-97019-7.
138. Barakou, I.; Sakalidis, K.E.; Abonie, U.S.; Finch, T.; Hackett, K.L.; Hettinga, F.J. Effectiveness of Physical Activity Interventions on Reducing Perceived Fatigue among Adults with Chronic Conditions: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. *Sci. Rep.* **2023**, *13*, 14582. https://doi.org/10.1038/s41598-023-41075-8.
139. Schöllhorn, I.; Stefani, O.; Lucas, R.J.; Spitschan, M.; Slawik, H.C.; Cajochen, C. Melanopic Irradiance Defines the Impact of Evening Display Light on Sleep Latency, Melatonin and Alertness. *Commun. Biol.* **2023**, *6*, 228. https://doi.org/10.1038/s42003-023-04598-4.
140. Wu, Y.; Ma, Y.; Cao, J.; Xie, R.; Chen, F.; Hu, W.; Huang, Y. Feasibility Study on the Use of "Qi-Tonifying Medicine Compound" as an Anti-Fatigue Functional Food Ingredient Based on Network Pharmacology and Molecular Docking. *Front. Nutr.* **2023**, *10*, 1131972. https://doi.org/10.3389/fnut.2023.1131972.
141. Dakpa, G.; Chiang, Y.-T.; Lin, L.-Y.; Tsao, N.-W.; Wang, C.-H.; Pérez-Sánchez, H.; Fernández, J.R.A.; Wang, S.-Y. Essential Oil-Derived Compounds Target Core Fatigue-Related Genes: A Network Pharmacology and Molecular Docking Approach. *PLoS ONE* **2025**, *20*, e0314125. https://doi.org/10.1371/journal.pone.0314125.
142. Zhu, H.; Wang, R.; Hua, H.; Cheng, Y.; Guo, Y.; Qian, H.; Du, P. Network Pharmacology Exploration Reveals Gut Microbiota Modulation as a Common Therapeutic Mechanism for Anti-Fatigue Effect Treated with Maca Compounds Prescription. *Nutrients* **2022**, *14*, 1533. https://doi.org/10.3390/nu14081533.
143. Ma, P.; Li, J.; Huang, Q.; Wei, S.; Ge, H.; Wang, Z. Exploring the Mechanism of Anti-Fatigue of Resveratrol Based on Network Pharmacology and Molecular Docking, and in Vitro Studies. *Sci. Rep.* **2023**, *13*, 2894. https://doi.org/10.1038/s41598-023-30141-w.
144. Niu, Q.; Li, H.; Tong, L.; Liu, S.; Zong, W.; Zhang, S.; Tian, S.; Wang, J.; Liu, J.; Li, B.; et al. TCMFP: A Novel Herbal Formula Prediction Method Based on Network Target's Score Integrated with Semi-Supervised Learning Genetic Algorithms. *Brief. Bioinform.* **2023**, *24*, bbad102. https://doi.org/10.1093/bib/bbad102.
145. Liu, Y.; Li, X.; Chen, C.; Ding, N.; Zheng, P.; Chen, X.; Ma, S.; Yang, M. TCMNPAS: A Comprehensive Analysis Platform Integrating Network Formulaology and Network Pharmacology for Exploring Traditional Chinese Medicine. *Chin. Med.* **2024**, *19*, 50. https://doi.org/10.1186/s13020-024-00924-y.
146. Adão Martins, N.R.; Annaheim, S.; Spengler, C.M.; Rossi, R.M. Fatigue Monitoring Through Wearables: A State-of-the-Art Review. *Front. Physiol.* **2021**, *12*, 790292. https://doi.org/10.3389/fphys.2021.790292.
147. Guo, D.; Wang, C.; Qin, Y.; Shang, L.; Gao, A.; Tan, B.; Zhou, Y.; Wang, G. Assessment of Flight Fatigue Using Heart Rate Variability and Machine Learning Approaches. *Front. Neurosci.* **2025**, *19*, 1621638. https://doi.org/10.3389/fnins.2025.1621638.
148. Daley, M.S.; Gever, D.; Posada-Quintero, H.F.; Kong, Y.; Chon, K.; Bolkhovsky, J.B. Machine Learning Models for the Classification of Sleep Deprivation Induced Performance Impairment During a Psychomotor Vigilance Task Using Indices of Eye and Face Tracking. *Front. Artif. Intell.* **2020**, *3*, 17. https://doi.org/10.3389/frai.2020.00017.
149. Wang, P.; Houghton, R.; Majumdar, A. Detecting and Predicting Pilot Mental Workload Using Heart Rate Variability: A Systematic Review. *Sensors* **2024**, *24*, 3723. https://doi.org/10.3390/s24123723.
150. Lhoste, C.; Quast, M.; Ronco, A.; Vogel, A.; Awai, C.E.; Branscheidt, M.; Lambercy, O.; Viskaitis, P.; Donegan, D.C. Closed-Loop Movement-Paired Transcutaneous Auricular Vagus Nerve Stimulation for Upper-Limb Rehabilitation: A Feasibility Study. *J. Neuroeng. Rehabil.* **2026**, *23*, 220. https://doi.org/10.1186/s12984-026-02021-7.
151. Zheng, D.-Y.; Ding, P.; Gong, M.; Zhu, H.-W.; Shi, H.-J.; Ren, G.-L.; Jin, L.-Y.; Wang, Y.-Q.; Yuan, H.-B.; Li, Y.-H. Transcutaneous Electrical Acupoint Stimulation vs Metoclopramide for Moderate to Severe Postoperative Nausea and Vomiting: A Randomized Clinical Trial. *JAMA Surg.* **2026**, *161*, 268–273. https://doi.org/10.1001/jamasurg.2025.6394.

152. Mayer, C.; Walch, O.; Dempsey, W.; Hannay, K.; Clingan, C.; Bowen, Z.; Rozwadowski, M.; Reichert, Z.R.; Henry, N.L.; Alumkal, J.J.; et al. A Circadian and App-Based Personalized Lighting Intervention for the Reduction of Cancer-Related Fatigue. *Cell Rep. Med.* **2025**, *6*, 102001. https://doi.org/10.1016/j.xcrm.2025.102001.
153. Park, M. Recent Advances in Wearable Thermal Devices for Virtual and Augmented Reality. *Micromachines* **2025**, *16*, 383. https://doi.org/10.3390/mi16040383.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.